Collaborative Project Proposal Summary **NACC FY2016**

Project title: Plasma biomarkers in Lewy Body Disease

Lead Investigator/Center: Neill Graff-Radford, MD / Mayo Clinic Jacksonville

Project work period: 7/1/2016 - 6/30/2018

Funding Period: 7/1/2016 - 6/30/2018

Collaborating Center (indicate non-ADC sites with asterisk)	**Project PI and degree(s)**	**Project budget (including indirect costs)**
Mayo Clinic Jacksonville	Neill Graff-Radford, MD	$ 144,133
University of North Texas Health Science Center	Sid O'Bryant, PhD	$ 55,365
University of Washington	Debby Tsuang, MD, MSc	$ 47,000
University of Texas at Dallas	John Hart, MD	$ 47,000
		$
		$
		$
		$
		$
		$
		$
		$
	Total funding requested:	$ 293,498

Department of Health and Human Services
Public Health Services

Grant Application

Do not exceed character length restrictions indicated.

LEAVE BLANK—FOR PHS USE ONLY.

Type	Activity	Number
Review Group		Formerly
Council/Board (Month, Year)		Date Received

1. TITLE OF PROJECT *(Do not exceed 81 characters, including spaces and punctuation.)*

Plasma biomarkers in Lewy Body Disease

2. RESPONSE TO SPECIFIC REQUEST FOR APPLICATIONS OR PROGRAM ANNOUNCEMENT OR SOLICITATION ☐ NO ☒ YES
(If "Yes," state number and title)

Number: NACC2016-COLLAB Title: NACC-funded Collaborative Projects, FY2016

3. PROGRAM DIRECTOR/PRINCIPAL INVESTIGATOR

3a. NAME (Last, first, middle)	3b. DEGREE(S)	3h. eRA Commons User Name
Petersen, Ronald C	MD, PhD	

3c. POSITION TITLE
Professor

3d. MAILING ADDRESS *(Street, city, state, zip code)*
200 First Street SW
Rochester, MN 55905-0001

3e. DEPARTMENT, SERVICE, LABORATORY, OR EQUIVALENT
Neurology

3f. MAJOR SUBDIVISION
Behavioral Neurology

3g. TELEPHONE AND FAX *(Area code, number and extension)*
TEL: 507-284-4006 FAX:

E-MAIL ADDRESS:
peter8@mayo.edu

4. HUMAN SUBJECTS RESEARCH	4a. Research Exempt	If "Yes," Exemption No.
☐ No ☒ Yes	☒ No ☐ Yes	

4b. Federal-Wide Assurance No.	4c. Clinical Trial	4d. NIH-defined Phase III Clinical Trial
00005001	☒ No ☐ Yes	☒ No ☐ Yes

5. VERTEBRATE ANIMALS ☒ No ☐ Yes — 5a. Animal Welfare Assurance No

6. DATES OF PROPOSED PERIOD OF SUPPORT *(month, day, year—MM/DD/YY)*		7. COSTS REQUESTED FOR INITIAL BUDGET PERIOD		8. COSTS REQUESTED FOR PROPOSED PERIOD OF SUPPORT	
From	Through	7a. Direct Costs ($)	7b. Total Costs ($)	8a. Direct Costs ($)	8b. Total Costs ($)
07/01/16	06/30/18	$44,551	$70,482	$91,089	$144,133

9. APPLICANT ORGANIZATION
Name Mayo Clinic Jacksonville
Address
4500 San Pablo Road
Jacksonville, FL 32224-1865

10. TYPE OF ORGANIZATION
Public: → ☐ Federal ☐ State ☐ Local
Private: → ☒ Private Nonprofit
For-profit: → ☐ General ☐ Small Business
☐ Woman-owned ☐ Socially and Economically Disadvantaged

11. ENTITY IDENTIFICATION NUMBER
1593337028A1
DUNS NO. 1532231510000 Cong. District FL-004

12. ADMINISTRATIVE OFFICIAL TO BE NOTIFIED IF AWARD IS MADE
Name Benjamin Ziemer
Title Institutional Official
Address Mayo Clinic Jacksonville
4500 San Pablo Road
Jacksonville, FL 32224-1865
Tel: 904-953-7173 FAX: 904-953-7134
E-Mail: flaresearchgrants@mayo.edu

13. OFFICIAL SIGNING FOR APPLICANT ORGANIZATION
Name Benjamin Ziemer
Title Institutional Official
Address Mayo Clinic Jacksonville
4500 San Pablo Road
Jacksonville, FL 32224-1865
Tel: 904-953-7173 FAX: 904-953-7134
E-Mail: flaresearchgrants@mayo.edu

14. APPLICANT ORGANIZATION CERTIFICATION AND ACCEPTANCE: I certify that the statements herein are true, complete and accurate to the best of my knowledge, and accept the obligation to comply with Public Health Services terms and conditions if a grant is awarded as a result of this application. I am aware that any false, fictitious, or fraudulent statements or claims may subject me to criminal, civil, or administrative penalties.

SIGNATURE OF OFFICIAL NAMED IN 13. *(In ink. "Per" signature not acceptable.)*

DATE

Use only if preparing an application with Multiple PDs/PIs. See http://grants.nih.gov/grants/multi_pi/index.htm for details.

Contact Program Director/Principal Investigator (Last, First, Middle): Petersen, Ronald C

3. PROGRAM DIRECTOR / PRINCIPAL INVESTIGATOR

3a. NAME (Last, first, middle)	3b. DEGREE(S)	3h. NIH Commons User Name
Graff-Radford, Neill R	MD	GRAFF1

3c. POSITION TITLE Professor	3d. MAILING ADDRESS *(Street, city, state, zip code)* Mayo Clinic Jacksonville 4500 San Pablo Road Jacksonville, FL 32224-1865
3e. DEPARTMENT, SERVICE, LABORATORY, OR EQUIVALENT Neurology	
3f. MAJOR SUBDIVISION Neurology	
3g. TELEPHONE AND FAX *(Area code, number and extension)* TEL: 904-953-7103 FAX: 904-953-7134	E-MAIL ADDRESS: graffradford.neill@mayo.edu

3. PROGRAM DIRECTOR / PRINCIPAL INVESTIGATOR

3a. NAME (Last, first, middle)	3b. DEGREE(S)	3h. NIH Commons User Name

3c. POSITION TITLE	3d. MAILING ADDRESS *(Street, city, state, zip code)*
3e. DEPARTMENT, SERVICE, LABORATORY, OR EQUIVALENT	
3f. MAJOR SUBDIVISION	
3g. TELEPHONE AND FAX *(Area code, number and extension)* TEL: FAX:	E-MAIL ADDRESS:

3. PROGRAM DIRECTOR / PRINCIPAL INVESTIGATOR

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3f. MAJOR SUBDIVISION	
3g. TELEPHONE AND FAX *(Area code, number and extension)* TEL: FAX:	E-MAIL ADDRESS:

3. PROGRAM DIRECTOR / PRINCIPAL INVESTIGATOR

3a. NAME (Last, first, middle)	3b. DEGREE(S)	3h. NIH Commons User Name

3c. POSITION TITLE	3d. MAILING ADDRESS *(Street, city, state, zip code)*
3e. DEPARTMENT, SERVICE, LABORATORY, OR EQUIVALENT	
3f. MAJOR SUBDIVISION	
3g. TELEPHONE AND FAX *(Area code, number and extension)* TEL: FAX:	E-MAIL ADDRESS:

PROJECT SUMMARY (See instructions):

The purpose of this project is to collect the requisite data and build the necessary collaborative relationships to submit a grant for a large-scale prospective study of the utility of blood-based biomarkers in Lewy Body disease (LBD). The long-term goal of this line of research is the generation of blood-based profiles that have diagnostic, prognostic and theragnostic value in LBD. Given the rapidly growing elderly population, neurodegenerative dementias are a major public health problem. LBD is the 2nd most prevalent neurodegenerative dementia accounting for 15-20% of cases and is often misdiagnosed as Alzheimer's disease (AD). LBD is an • -synuclein disorder that is characterized by Lewy Body and Lewy neurites in specific areas of the brain as well as acetylcholine neuronal degeneration. There is frequent AD and LBD overlap making the differential diagnosis between LBD and AD a significant problem in clinical practice. Additionally, there is an urgent need for methods to predict clinical course in LBD to design trials and monitor interventions. Based on preliminary findings it is our hypothesis that a blood-based biomarker profile can be accurate in detecting and distinguishing LBD from AD and controls. The Specific Aims of this project are as follows: Specific Aim 1 – Replicate our blood-based profile of LBD in a larger sample and Specific Aim 2 – To identify biologically-based subgroups in LBD.
Lewy

RELEVANCE (See instructions):

Lewy body disease is hard to distinguish from Alzheimer disease because the pathologies overlap. Based on promising preliminary data this study evaluates if a blood based biomarker is able to able to have diagnostic, therapeutic and pathogenic use.

PROJECT/PERFORMANCE SITE(S) (if additional space is needed, use Project/Performance Site Format Page)

Project/Performance Site Primary Location			
Organizational Name: Mayo Clinic Jacksonville			
DUNS: 1532231510000			
Street 1: 4500 San Pablo Road		Street 2:	
City: Jacksonville	County: Duval		State: FL
Province:	Country: USA		Zip/Postal Code: 32224-1865
Project/Performance Site Congressional Districts: FL-004			

Additional Project/Performance Site Location			
Organizational Name: Mayo Clinic			
DUNS: 006471700			
Street 1: 200 First Street SW		Street 2:	
City: Rochester	County:		State: MN
Province:	Country: USA		Zip/Postal Code: 55905-0001
Project/Performance Site Congressional Districts: MN-001			

SCIENTIFIC/KEY PERSONNEL. See instructions. *Use continuation pages as needed* to provide the required information in the format shown below. Start with Program Director(s)/Principal Investigator(s). List all other key personnel in alphabetical order, last name first.

Name	eRA Commons User Name	Organization	Role on Project
Graff-Radford, Neill R, MD	GRAFF1	Mayo Clinic Jacksonville	PD/PI
Boeve, Bradley F, MD	BOEVE1	Mayo Clinic	Site PI
Mielke, Michelle M, PhD	MMIELKE1	Mayo Clinic	Co-Investigator

OTHER SIGNIFICANT CONTRIBUTORS

Name	Organization	Role on Project

Human Embryonic Stem Cells ☒ **No** ☐ **Yes**

If the proposed project involves human embryonic stem cells, list below the registration number of the specific cell line(s) from the following list: http://stemcells.nih.gov/research/registry/eligibilityCriteria.asp. *Use continuation pages as needed.*

If a specific line cannot be referenced at this time, include a statement that one from the Registry will be used.

Cell Line

Program Director/Principal Investigator (Last, First, Middle): Petersen, Ronald C

DETAILED BUDGET FOR INITIAL BUDGET PERIOD DIRECT COSTS ONLY	FROM	THROUGH
	7/1/2016	6/30/2017

List PERSONNEL *(Applicant organization only)*
Use Cal, Acad, or Summer to Enter Months Devoted to Project
Enter Dollar Amounts Requested *(omit cents)* for Salary Requested and Fringe Benefits

NAME	ROLE ON PROJECT	Cal. Mnths	Acad. Mnths	Summer Mnths	INST.BASE SALARY	SALARY REQUESTED	FRINGE BENEFITS	TOTAL
Graff-Radford, Neill R, MD	PD/PI	0.12			185,100	1,851	466	2,317
TBN Study Coordinator	Coordinator	1.76			56,720	8,338	3,502	11,840
Boeve, Bradley, MD	PD/PI	0.12			185,100	1,851	522	2,373
Gearhart, Debra	Study Coordinator	0.78			63,415	4,116	1,391	5,507
Jacobson-Butrum, Kelly	Psychometrist	0.78			59,601	3,868	1,307	5,175
SUBTOTALS →						20,024	7,188	27,212

CONSULTANT COSTS	
EQUIPMENT *(Itemize)*	
SUPPLIES *(Itemize by category)*	
TRAVEL	
INPATIENT CARE COSTS	
OUTPATIENT CARE COSTS	
ALTERATIONS AND RENOVATIONS *(Itemize by category)*	
OTHER EXPENSES *(Itemize by category)*	
Plasma Assays (Rochester)	17,500
CONSORTIUM/CONTRACTUAL COSTS	DIRECT COSTS
SUBTOTAL DIRECT COSTS FOR INITIAL BUDGET PERIOD *(Item 7a, Face Page)*	$ 44,712
CONSORTIUM/CONTRACTUAL COSTS	FACILITIES AND ADMINISTRATIVE COSTS
TOTAL DIRECT COSTS FOR INITIAL BUDGET PERIOD	$ 44,712

BUDGET FOR ENTIRE PROPOSED PROJECT PERIOD
DIRECT COSTS ONLY

BUDGET CATEGORY TOTALS	INITIAL BUDGET PERIOD *(from Form Page 4)*	2nd ADDITIONAL YEAR OF SUPPORT REQUESTED	3rd ADDITIONAL YEAR OF SUPPORT REQUESTED	4th ADDITIONAL YEAR OF SUPPORT REQUESTED	5th ADDITIONAL YEAR OF SUPPORT REQUESTED
PERSONNEL: *Salary and fringe benefits. Applicant organization only.*	27,212	28,877			
CONSULTANT COSTS					
EQUIPMENT					
SUPPLIES					
TRAVEL					
INPATIENT CARE COSTS					
OUTPATIENT CARE COSTS					
ALTERATIONS AND RENOVATIONS					
OTHER EXPENSES: Plasma Assays	17,500	17,500			
DIRECT CONSORTIUM/ CONTRACTUAL COSTS					
SUBTOTAL DIRECT COSTS *(Sum = Item 8a, Face Page)*	44,712	46,377			
F&A CONSORTIUM/ CONTRACTUAL COSTS					
TOTAL DIRECT COSTS	44,712	46,377			

TOTAL DIRECT COSTS FOR ENTIRE PROPOSED PROJECT PERIOD	**$** 91,089

JUSTIFICATION. Follow the budget justification instructions exactly. Use continuation pages as needed.

Mayo Clinic Jacksonville Budget Justification

SENIOR/KEY PERSONNEL

Neill Graff-Radford, MD, PD/PI (0.12 calendar months in years 1-2): Dr. Graff-Radford (with Dr. O'Bryant) will be the overall PI and the Mayo Jacksonville clinical PI. As the overall PI he will arrange the the monthly PI teleconferences. Dr. Graff-Radford will help the with the analyses of the data and draft the initial final description manuscripts. He will work with other investigators to draft other scientific manuscripts.

OTHER PERSONNEL

TBN Study Coordinator, Site Coordinator, (1.89 calendar months in years 1-2): We shall recruit an experienced monitor who will help recruit the patients, consent them, collect the NACC data and enter it into the NACC data base. The coordinator will help process the blood specimens, label and store them and when appropriate ship them to Rochester and UTSW.

Mayo Clinic Rochester Budget Justification

SENIOR/KEY PERSONNEL
Bradley F. Boeve, M.D. – Principal Investigator (0.12 calendar months, Years 1 and 2).
Dr. Boeve is a neurologist with expertise in behavioral neurology, sleep medicine and movement disorders. He has conducted the neurological evaluations for many of the ADRC participants and will continue to do so in the proposed study. He will provide expertise in the study on the clinical and pathological aspects of Dementia with Lewy Bodies (DLB). He will be involved in the preparation of abstracts for presentation and manuscripts for publication.

Michelle M. Mielke, Ph.D. – Co-Investigator (0.12 calendar months, Year 2 only).
Dr. Mielke is an epidemiologist trained in both neuroscience and psychiatric epidemiology. She is the PI of several NIH-funded clinical- and epidemiological-based grants examining biomarkers for the development and progression of neurodegenerative disease. She has also recently received grants from the Lewy Body Dementia Association and the Michael J. Fox Foundation. A major focus of her work has been to examine plasma sphingolipids as risk factors and biomarkers for the onset and progression of neurodegenerative diseases. Dr. Mielke will oversee all aspects of the study at Mayo-Rochester and with regards to the sphingolipids. She will contribute to manuscripts, abstracts, progress reports, and presentation of findings.

OTHER PERSONNEL
Debra Gearhart, Clinical Research Coordinator (0.78 calendar months).
Ms. Gearhart will be responsible for obtaining participant consent, maintaining the study's IRB approvals, participating in monthly conference calls, administering the study questionnaires, data entry, and training other ADRC staff regarding the study's protocol.

Kelly Jacobson-Butrum, Psychometrist (0.78 calendar months).
Ms. Jacobson-Butrum will administer and score the neuropsychological battery of tests associated with the UDS and other psychometric measures for this project.

OTHER EXPENSES
A total of $140 per sample has been allocated for serum plasma assays to be performed in the core laboratory in Rochester. Approximately 125 samples will be measured each year for a total cost of $17,500 per year.

OMB No. 0925-0001/0002 (Rev. 08/12 Approved Through 8/31/2015)

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FIVE PAGES**.

NAME: Graff-Radford, Neill R, MBBCh, FRCP(London)

eRA COMMONS USER NAME (credential, e.g., agency login): GRAFF1

POSITION TITLE: Professor of Neurology, Mayo College of Medicine

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	YEAR(s)	FIELD OF STUDY
University of Witwatersrand, South Africa	MBBCh	1973	Medicine
Royal College of Physicians (UK)	MRCP (UK)	1978	Internal Medicine
University of Colorado Health Science Center	Residency	1981	Neurology
University of Iowa hospital and Clinics	Fellowship	1982	Behavioral Neurology

A. Personal Statement

1. For this multicenter study I have the expertise, leadership and motivation to successfully carry out the project. I have worked in the area of dementia research for 32 years and being doing clinical trials since 1991. I have played a leadership role as Chair of the Department of Neurology at Mayo Jacksonville from 1994 to 2004. I have worked in the area of biomarkers and Lewy Body disease for more than 15 years. One of our initial studies published in Science linked plasma Ab levels to an area on chromosome 10[1]. We also reported the hereditary factors related to plasma Aβ[2] and the risk developing dementia as there is a drop in plasma Aβ42 while Aβ40 remains high[3]. More recently with Dr. Rademakers we have shown that plasma Progranulin levels are an excellent way to detect persons with Progranulin mutations[4]. To date I have published 26 papers pertaining to Lewy Body disease. Please see my publications.. I am now part of a consortium working on standardization of plasma biomarkers including Dr. Sid O'Bryant who is the co PI on this study

1. Ertekin-Taner N, Graff-Radford N, Younkin LH, et al. Linkage of plasma Abeta42 to a quantitative locus on chromosome 10 in late-onset Alzheimer's disease pedigrees. Science 2000;290:2303-4.
2. Ertekin-Taner N, Younkin LH, Yager DM, et al. Plasma amyloid beta protein is elevated in late-onset Alzheimer disease families. Neurology 2008;70:596-606.
3. Graff-Radford NR, Crook JE, Lucas J, et al. Association of low plasma Abeta42/Abeta40 ratios with increased imminent risk for mild cognitive impairment and Alzheimer disease. Archives of Neurology 2007;64:354-62.
4. Finch N, Baker M, Crook R, et al. Plasma progranulin levels predict progranulin mutation status in frontotemporal dementia patients and asymptomatic family members. Brain : a journal of neurology 2009;132:583-91..

1. Positions and Honors:

Positions and Employment

1982 - 87 Assistant Professor, Deprtment of Neurology, University of Iowa Hospitals & Clinics
1987 - 89 Associate Professor, Department of Neurology, University of Iowa Hospitals & Clinics
1989 - 94 Associate Professor, Department of Neurology, Mayo Medical School, Rochester, MN
1994 - 04 Chair, Department of Neurology, Mayo Clinic, Jacksonville, FL
1994 - Professor, Department of Neurology, Mayo Medical School, Rochester, MN

Other Experience and Professional Memberships

1978 - Member, Royal College of Medicine (London)
1986 - Fellow, American Academy of Neurology
1990 -2008 Examiner (1990-2004), Sr Examiner (2002-2008), American Board of Psychiatry & Neurology
1991 - American Neurological Association

2001 -	Fellow, Royal College of Medicine (London)
1996 -	Member of the Alzheimer's Disease Cooperative Study Advisory group
2002 - 07	Abstract Reviewer, American Academy of Neurology
2004 - 07	Topic Chair For Aging and Dementia, American Academy of Neurology
2005 - 09	Course Director Full Day Course, Update on Dementia
2009 -2013	Course Director in the American Academy of Neurology MCI course
2007 -	Science Committee, American Academy of Neurology
2006 - 09	Executive Committee Member, Alzheimer's Disease Reseaerch Centers (ADRCs)
2008 - 09	Chair of the Executive Committee, Alzheimer's Disease Research Centers (ADRCs)

Honors

1983	A Certificate of Honorable Mention, "Nonhemorrhagic Thalamic Infarctions: Neuropsychological, Anatomical and Neurophysiological Correlates" - S. Weir Mitchell Award Competition
1996 - 02	Appointed by the Governor and served for six years on the Board of the Florida State Alzheimer's Disease Initiative (ADI)
2001	Elected to be a Fellow, Royal College of Physicians, London
2012 -2014	Blue Ribbon Task Force for Alzheimer Disease for the State of Florida
2014-	Member of the Alzheimer Disease Research Grant Advisory Board for State of Florida

C. Contribution to Science

2. My earlier publications described the neurological syndromes related to non-hemorrhagic strokes in the **thalamus**[5]. I then went onto describe the anatomical basis of diencephalic **amnesia**[6]. With Dr. Damasio we described the clinical picture including memory loss with basal forebrain stroke[7]. Also in my early work I had one of the first descriptions, longitudinal findings and autopsy description of a patient with what later became known as semantic dementia[8]. All of these and many similar publications prepared me for studying patients with higher cortical deficits in degenerative dementia.

5. Graff-Radford NR, Damasio H, Yamada T, Eslinger PJ, Damasio AR. Nonhaemorrhagic thalamic infarction. Clinical, neuropsychological and electrophysiological findings in four anatomical groups defined by computerized tomography. Brain : a journal of neurology 1985;108 (Pt 2):485-516.
6. Graff-Radford NR, Tranel D, Van Hoesen GW, Brandt JP. Diencephalic amnesia. Brain : a journal of neurology 1990;113 (Pt 1):1-25.
7. Damasio AR, Graff-Radford NR, Eslinger PJ, Damasio H, Kassell N. Amnesia following basal forebrain lesions. Archives of Neurology 1985;42:263-71.
8. Graff-Radford NR, Damasio AR, Hyman BT, et al. Progressive aphasia in a patient with Pick's disease: a neuropsychological, radiologic, and anatomic study. Neurology 1990;40:620-6.

3. My first clinical trial was in **Normal Pressure Hydrocephalus** (NPH)[9]. This was one of the first prospective studies in this disease and we showed that cerebrospinal fluid (CSF) conductance (absorption of CSF at different CSF pressures was not specific for deciding which NPH patients would improve with shunt surgery. In this paper we developed methodology and how to gage if persons improved after shunt surgery and many other investigators have used similar or modified our methods of doing this. We have shown systemic hypertension is associated with NPH and more recently that pulse pressure and systolic pressure are associated with increased ventricular enlargement[10]. Further our studies have shown that patients with NPH have large heads in more than 10% of cases indicating that a congenital component plays a role in the syndrome. Recently we reported that the lumbar puncture pressure should be used to set the valve opening pressure which may avoid overdrainage with shunt surgery[11]. Most recently we have published an hypothesis why CSF Alzheimer biomarkers may be misleading in trying to determine if NPH patients have co-morbid AD[12].

9. Graff-Radford NR, Godersky JC, Jones MP. Variables predicting surgical outcome in symptomatic hydrocephalus in the elderly. Neurology 1989;39:1601-4.
10. Graff-Radford NR, Knopman DS, Penman AD, Coker LH, Mosley TH. Do systolic BP and pulse pressure relate to ventricular enlargement? Eur J Neurol 2013;20:720-4.
11. Khan QU, Wharen RE, Grewal SS, et al. Overdrainage shunt complications in idiopathic normal-pressure hydrocephalus and lumbar puncture opening pressure. Journal of neurosurgery 2013;119:1498-502.

12. Graff-Radford NR. Alzheimer CSF biomarkers may be misleading in normal-pressure hydrocephalus. Neurology 2014;83:1573-5.

4. At Mayo I was able to collect larger cohorts of Caucasian and African American Alzheimer disease (more than 1200), Lewy Body disease (more than 200) and Frontotemporal dementia cases (more than 300) and many controls (more than 1600). With these I have had the privilege of working with **Mayo geneticists** such as Rosa Rademakers (with whom I have published 56 papers) and Steven Younkin (with whom I have published 55 papers) and Nilufer Ertekin-Taner (with whom I have published 38 papers). Many of the cases I collected have been included in the national and international consortia that have discovered more than 20 candidate genes for Late Onset Alzheimer Disease (LOAD). Some examples of our publications include one of the earliest GWAS studies in LOAD[13], the discovery of C9ORF72[18], the GWAS for LOAD in African Americans[19].

17. Carrasquillo MM, Zou F, Pankratz VS, et al. Genetic variation in PCDH11X is associated with susceptibility to late-onset Alzheimer's disease. Nature Genetics 2009;41:192-8.
18. DeJesus-Hernandez M, Mackenzie IR, Boeve BF, et al. Expanded GGGGCC hexanucleotide repeat in noncoding region of C9ORF72 causes chromosome 9p-linked FTD and ALS. Neuron 2011;72:245-56.
19. Reitz C, Jun G, Naj A, et al. Variants in the ATP-binding cassette transporter (ABCA7), apolipoprotein E 4,and the risk of late-onset Alzheimer disease in African Americans. JAMA 2013;309:1483-92.

5. **Clinicopathological studies**. When I move to Mayo I established a brain bank and we have followed more than 450 cases and controls clinically to autopsy. Dr. Dickson moved to Mayo Jacksonville in 1998 and he and I have co-authored 114 papers many clinicopathological studies. Examples of this include our study showing that posterior cortical atrophy is most often due to Alzheimer disease[14], that hippocampal sclerosis can be mistaken for Alzheimer disease clinically[15], that Alzheimer pathology can be grouped into typical, limbic and hippocampal sparing and the clinical picture and progression is different between these groups[16]

20. Tang-Wai DF, Graff-Radford NR, Boeve BF, et al. Clinical, genetic, and neuropathologic characteristics of posterior cortical atrophy. Neurology 2004;63:1168-74.
21. Pao WC, Dickson DW, Crook JE, Finch NA, Rademakers R, Graff-Radford NR. Hippocampal sclerosis in the elderly: genetic and pathologic findings, some mimicking Alzheimer disease clinically. Alzheimer disease and associated disorders 2011;25:364-8.
22. Murray ME, Graff-Radford NR, Ross OA, Petersen RC, Duara R, Dickson DW. Neuropathologically defined subtypes of Alzheimer's disease with distinct clinical characteristics: a retrospective study. Lancet Neurol 2011.

Complete List of Published Work in My Bibliography:
http://www.ncbi.nlm.nih.gov/sites/myncbi/neill.graff-radford.1/bibliography/47339120/public/?sort=date&direction=ascending.

D. Research Support

Ongoing Research Support

U01AG24904-7 (Graff-Radford) 06/01/2005 – 08/31/2016
National Institute of Aging
Alzheimer Disease Neuroimaging Initiative - Clinical Trial (Subcontract on U01 AG 24904 at UCSD)
The major goal of this clinical trial is to evaluate the use of MRI and PET scan in predicting conversion from MCI to AD and related these radiological measures to AD biomarkers in the CSF and plasma.
Role: Site PD/PI

P50AG 16574-14 (Graff-Radford) 05/01/2014 – 04/30/2019
National Institute of Aging
ADRC Jacksonville Consortiums years 16-20
The major goal is to examine the epidemiology of Alzheimer's disease (AD) and the clinical, imaging, and neuropathology of the boundary between normal aging and early AD.
Role: Site PD/PI

U01AG032438-1 (Graff-Radford) 01/01/2012 – 12/31/2017

National Institute of Aging
DIAN - Dominantly Inherited Alzheimer Network (Subaward w/Dr John Morris' U01 AG032438 Collaborative Agreement at Washington University in St Louis)
The major goal is to study dominantly inherited Alzheimer's disease.
Role: Site PD/PI

R01AG041797-1 (Graff-Radford) 04/01/2012 – 03/31/2017
National Institute of Health
Epidemiology of Familial Late-Onset Alzheimer's Disease (Subcontract w/Dr Mayeux's R01 AG041651 grant at Columbia University Medical Center)
The major goal is to validate and quantify the clinical impact of SNPs in PICALM, CLU, BIN1, MS4A gene clusters, CD33, CD2AP, ABCA7 and EPHA1 using the multiplex families recruited NIA-LOAD.
Role: Site PD/PI

R01AG039389-1 (Graff-Radford) 04/15/2012 – 04/14/2014
National Institute of Aging
A Blood-Based Screening Tool for Alzheimer's Disease (subcontract w/Dr Sid O'Bryant's NIH R01 resubmission at TTUHSC)
The major goal is validate a blood-based screening tool for Alzheimer's Disease
Role: Site PD/PI

Grant Number: N/A (Graff-Radford) 11/16/2012 – 11/16/2014
CR20
Exercise in Asymptomatic Pre Alzheimer Disease
This grant preliminarily studies the effect that exercise has on asymptomatic pre-Alzheimer's disease
Role: PD/PI

Grant Number N/A (Graff-Radford) 12/18/2013 – 06/17/2016
Eli Lilly and Company
Effect of Passive Immunization on the Progression of Mild Alzheimer's Disease: Solanezumab (LY2062430) Vs Placebo
This grant studies passive immunization on the Progression of Mild Alzheimer's Disease
Role: PD/PI

U01AG041845 (Graff-Radford) 03/01/2013 – 02/28/2015
NIH
Therapeutic effects of intranasally-administered insulin in adults with amnestic mild cognitive impairment (aMCI) or mild Alzheimer?s disease (AD) ADC-046-INI (Sub w/P Aisen's UCSD Sub w/S Craft's NIH SNIFF Trial Cooperative Agrmt at Wake Forest)
This study evaluates the effects of intranasally-administered insulin in adults with amnestic mild cognitive impairment (aMCI) or mild Alzheimer's disease
Role: Site PD/PI

U19AG010483 (Graff-Radford) 12/31/2013 – 11/30/2015
NIH
Anti-amyloid treatment in asymptomatic Alzheimer's Disease (A4 Study) (Subaward w/Dr P Aisen's NIH U19AG010483 at UCSD)
This study investigates anti-amyloid treatment in asymptomatic Alzheimer's Disease
Role: Site PD/PI

Completed Research Support

R01AG15922-7-6 (Graff-Radford) 09/30/2003 – 07/31/2010
National Institute of Aging
A Randomized Trial of Estrogen to Delay Alzheimer's Disease in Women at Risk
The major goal was to see if hormone replacement therapy could prevent Alzheimer disease
Role: PD/PI

AG26395-5 (Graff-Radford) 07/01/2005 – 06/30/2011
National Institute of Aging

Genetics Consortium for Late Onset Alzheimers Disease (LOAD Study)Dr. R. Mayeux, Columbia University
The major goal was to collect 1000 multiplex AD families to evaluate the genetic of Late Onset Alzheimer's Disease.
Role: Site PD/PI

R01AG15866-10 (Ferman) 09/30/2005 – 04/30/2011
National Institute of Aging
Neuropsychology of Dementia with Lewy Bodies
The major goal was to characterize neurobehavioral features of DLB
Role: Co-Investigator

RC2AG036535-2 (Graff-Radford) 09/30/2009 – 08/31/2012
National Institute of Aging
Alzheimer's Disease Neuroimaging Initiative- Grand Opportunity (ADNI-GO) (Sub w/Dr M Weiner at UCSD who has sub w/Northern California Institute for Research & Education's RC2 AG036535)
The major goal was to create a data base on which future clinical trails could be planned
Role: Site PD/PI

U01AG010483-1 (Graff-Radford) 07/01/2011 – 06/30/2012
National Institute of Aging
Subaward w/Dr P Aisen's U01AG010483 at UCSD entitled "ADCS Infrastructure Support"
The major goal was to study the effect of Resveratrol Treatment in Patients with Mild to Moderate Alzheimer's Disease.
Role: Site PD/PI

R01AG 06656-21 (Younkin) 09/15/2007 – 05/31/2013
National Institute of Aging
AChE, ChaT, & Cholinergic Neurons in Aging and AD
The major goal of this project was to determine if plasma Aß levels might serve as useful biomarkers for identifying individuals at risk for Alzheimer's disease.
Role: Co-Investigator

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. DO NOT EXCEED FIVE PAGES.

NAME: Boeve, Bradley F.

eRA COMMONS USER NAME (credential, e.g., agency login): boeve1

POSITION TITLE: Professor of Neurology

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
University of Florida, Gainesville, FL	B.S.	12/1986	Psychology
University of Florida, Gainesville, FL	M.D.	05/1991	Medicine
Mayo Clinic, Rochester, MN	Internship	06/1992	Medicine
Mayo Clinic, Rochester, MN	Residency	06/1995	Neurology
Mayo Clinic, Rochester, MN	Fellowship	06/1996	Behavioral Neurology
Mayo Clinic, Rochester, MN	Fellowship	12/1996	Sleep Medicine

A. Personal Statement

I am a neurologist with subspecialty training in behavioral neurology and sleep medicine. Over the past 20 years I have been particularly interested in the clinical, sleep, neuropsychological, genetic, neuroimaging, and neuropathologic aspects of the neurodegenerative disorders which manifest as cognitive impairment and/or parkinsonism – namely mild cognitive impairment, Alzheimer's disease, dementia with Lewy bodies, Parkinson's disease, frontotemporal dementia +/- parkinsonism, corticobasal syndrome/corticobasal degeneration, and progressive supranuclear palsy. I have worked with many colleagues in the Mayo Alzheimer's Disease Research Center (ADRC), Mayo Clinic Study of Aging, Mayo Center for Sleep Medicine, Morris K. Udall Center of Excellence for Parkinson's Disease Research, and Mayo Clinic Sports Medicine Center. I trust that my training, experience and interests will combine to contribute to the success of this application.

B. Positions and Honors

Positions and Employment

1997 – 1999 Senior Associate Consultant, Department of Neurology, Mayo Clinic Rochester
1999 – 2003 Assistant Professor of Neurology, Mayo Medical School
2000 – present Consultant, Department of Neurology, Mayo Clinic Rochester
2000 – present Chair, Division of Behavioral Neurology, Mayo Foundation
2000 – present Director, Behavioral Neurology Fellowship Program, Mayo Clinic Rochester
2002 – present Head, Section of Behavioral Neurology, Mayo Clinic Rochester
2003 – 2008 Associate Professor of Neurology, Mayo Clinic College of Medicine
2008 – present Professor of Neurology, Mayo Clinic College of Medicine

Other Experience and Professional Memberships

Member: American Medical Association, American Academy of Neurology, American Neurological Association, American Academy of Sleep Medicine, Movement Disorders Society, Society for Behavioral and Cognitive Neurology, Alzheimer's Association International Society to Advance Alzheimer's Research and Treatment (ISTAART), International Society for Frontotemporal Dementias

Scientific Advisory Panels: International Classification of Sleep Disorders - Parasomnia Nosology Revision Committee (2003-2005); Scientific Advisory Council, Lewy Body Dementia Association (2004-present); Medical Advisory Council, Association for Frontotemporal Degeneration (2005-present, Chair 2007-2011); International REM Sleep Behavior Disorder Study Group (2008-present); Medical and Scientific Advisory Board, Minnesota-

North Dakota Chapter, Alzheimer's Association (2009-2011); National Football League, Head Neck and Spine Committee, Subcommittee on Retired Players (2010-present); Advisory Panel on Lewy Body Disease, Diagnostic and Statistical Manual – 5th Edition (2011-2012); Scientific Advisory Board, Tau Consortium (2011-present)

NIH Service: Ad hoc Reviewer, NIA and NINDS, various Study Sections (2005-present); Ad hoc Reviewer, National Alzheimer's Coordinating Center (2008); Ad hoc Reviewer, various Alzheimer's Disease Center programs (2003-present); International Workshop on Brain Banking, NINDS (2002); Workshop on Frontotemporal Dementia, NINDS (2007); Workshop on Frontotemporal Dementia/Progranulin, NINDS (2008); Frontotemporal Dementia Common Data Elements Workshop, NINDS/NIA (2010); Biomarkers for Lewy Body Disease Conference, NINDS (2010); Advances in ALS and FTD Genetics Workshop, NINDS (2014)

Honors

1991	Graduation with Honors for Academic Achievement, and for Special Achievement, College of Medicine, University of Florida
1996	Henry W. Woltman Award for Excellence in Clinical Neurology, Department of Neurology, Mayo Clinic
2002, 2003	Excellence in Teaching, Mayo Medical School
2003	Karis Award, Mayo Foundation

C. Contribution to Science

Five of my most significant contributions to science are described below. The overarching theme of my work involves the clinical, sleep, neuropsychological, genetic, neuroimaging and neuropathologic characterization of neurodegenerative diseases, with particular areas of interest being on 1) prodromal or early manifestations of neurodegenerative diseases, 2) longitudinal characterization of symptomatic and prodromal/asymptomatic individuals in preparation for future disease-modifying therapeutic trials, and 3) neurogenetics.

1. Characterization of the clinical syndromes associated with Lewy body disease (LBD) pathology, with the particular focus on dementia with Lewy bodies (DLB)

I have been involved in the clinical, sleep, neuropsychological, genetic, neuroimaging, and neuropathologic characterization of DLB since 1997 (over 80 publications). Some of my contributions to the field include: the observation of REM sleep behavior disorder (RBD) being strongly associated with DLB; the identification of the neuropsychological profile of impairment in DLB; the characterization of the key management considerations in addressing the cognitive, neuropsychiatric, motor, sleep, autonomic and sensory manifestations of DLB; contributing to the consensus criteria for the clinical and neuropathologic diagnosis of DLB; the observation of hypersomnolence being frequent and prominent in DLB patients; and contributing to the knowledge on the neuroimaging signatures of DLB. I was also one of the organizers of the International DLB Conference held in Fort Lauderdale, Florida, in December 2015.

1. **Boeve BF**, Silber MH, Ferman TJ, Kokmen E, Smith GE, Ivnik RJ, Parisi JE, Olson E, Petersen RC. REM sleep behavior disorder and degenerative dementia: An association likely reflecting Lewy body disease. *Neurology* 1998;51:363-370.
2. McKeith IG, Dickson DW, Lowe J, Emre M, O'Brien JT, Feldman H, Cummings J, Duda JE, Lippa C, Perry EK, Aarsland D, Arai H, Ballard CG, **Boeve BF**, Burn DJ, Costa D, Del Ser T, Dubois B, Galasko D, Gauthier S, Goetz CG, Gomez-Tortosa E, Halliday G, Hansen LA, Hardy J, Iwatsubo T, Kalaria RN, Kaufer D, Kenny RA, Korczyn A, Kosaka K, Lee V M-Y, Lees A, Litvan I, Londos E, Lopez OL, Minoshima S, Mizuno Y, Molina JA, Mukaetova-Ladinska EB, Pasquier F, Perry RH, Schulz JB, Trojanowski JQ, Yamada M, for the Consortium on DLB. Dementia with Lewy bodies: Diagnosis and management: Third report of the DLB Consortium. Neurology 2005;65:1863–1872.
3. Kantarci K, Lowe VJ, **Boeve BF**, Weigand SD, Senjem ML, Przybelski SA, Dickson DW, Parisi JE, Knopman DS, Smith GE, Ferman TJ, Petersen RC, Jack CR Jr. Multimodality imaging characteristics of dementia with Lewy bodies. *Neurobiol Aging.* 2012 Sep;33(9):2091-105.
4. Ferman TJ, Smith GE, Dickson DW, Graff-Radford NR, Lin SC, Wszolek Z, Van Gerpen JA, Uitti R, Knopman DS, Petersen RC, Parisi JE, Silber MH, **Boeve BF**. Abnormal daytime sleepiness in dementia with Lewy bodies compared to Alzheimer's disease using the Multiple Sleep Latency Test. *Alzheimers Res Ther*. 2014 Dec 10;6(9):76.

2. Characterization of the clinical syndromes associated with frontotemporal lobar degeneration (FTLD) pathology, with the particular focus on behavioral variant frontotemporal dementia (bvFTD), primary progressive aphasia (PPA), corticobasal syndrome (CBS) and progressive supranuclear palsy (PSP)

I have been involved in the clinical, sleep, neuropsychological, genetic, neuroimaging, and neuropathologic characterization of FTLD-spectrum disorders since 1999 (over 100 publications). Some of my contributions to the field include: the observation of clinicopathologic heterogeneity in CBS and corticobasal degeneration; characterizing the similarities and differences between the FTLD-spectrum disorders; contributing to the consensus criteria for the clinical diagnosis of bvFTD; contributing to the drug development program plans for symptomatic and future disease-modifying therapies in FTLD.

1. **Boeve BF**. Links between frontotemporal lobar degeneration, corticobasal degeneration, progressive supranuclear palsy, and amyotrophic lateral sclerosis. Alzheimer Dis Assoc Disord 2007;21:31-38.
2. Knopman DS, Jack CR Jr, Kramer JH, **Boeve BF**, Caselli RJ, Graff-Radford NR, Mendez MF, Miller BL, Mercaldo ND. Brain and ventricular volumetric changes in frontotemporal lobar degeneration over 1 year. *Neurology* 2009; May 26;72(21):1843-9.
3. Rascovsky K, Hodges JR, Knopman D, Mendez MF, Kramer JH, Neuhaus J, van Swieten JC, Seelaar H, Dopper EG, Onyike CU, Hillis AE, Josephs KA, **Boeve BF**, Kertesz A, Seeley WW, Rankin KP, Johnson JK, Gorno-Tempini ML, Rosen H, Prioleau-Latham CE, Lee A, Kipps CM, Lillo P, Piguet O, Rohrer JD, Rossor MN, Warren JD, Fox NC, Galasko D, Salmon DP, Black SE, Mesulam M, Weintraub S, Dickerson BC, Diehl-Schmid J, Pasquier F, Deramecourt V, Lebert F, Pijnenburg Y, Chow TW, Manes F, Grafman J, Cappa SF, Freedman M, Grossman M, Miller BL. Sensitivity of revised diagnostic criteria for the behavioural variant of frontotemporal dementia. *Brain.* 2011 Sep;134(Pt 9):2456-77.
4. Boxer AL, Gold M, Huey E, Hu WT, Rosen H, Kramer J, Gao FB, Burton EA, Chow T, Kao A, Leavitt BR, Lamb B, Grether M, Knopman D, Cairns NJ, Mackenzie IR, Mitic L, Roberson ED, Van Kammen D, Cantillon M, Zahs K, Jackson G, Salloway S, Morris J, Tong G, Feldman H, Fillit H, Dickinson S, Khachaturian ZS, Sutherland M, Abushakra S, Lewcock J, Farese R, Kenet RO, Laferla F, Perrin S, Whitaker S, Honig L, Mesulam MM, **Boeve B**, Grossman M, Miller BL, Cummings JL. The advantages of frontotemporal degeneration drug development (part 2 of frontotemporal degeneration: The next therapeutic frontier). *Alzheimers Dement.* 2013 Mar;9(2):189-98.

3. Characterization of REM sleep behavior disorder

I have been involved in the clinical, management, imaging and neuropathologic aspects of RBD since 1997 (over 50 publications). Some of my contributions to the field include: the observation that RBD is particularly associated with the synucleinopathies; the characterization of RBD occurring years or decades prior to the evolution of cognitive impairment and/or dementia; observational experience on the therapeutic approaches to managing RBD; development of screening measures for RBD; epidemiologic study of RBD in a population-based cohort; and characterization of planning for future disease-modifying therapeutic trials potentially delaying or preventing the evolution of RBD to mild cognitive impairment/dementia with Lewy bodies or Parkinson's disease.

1. **Boeve BF**. REM sleep behavior disorder: Updated review of the core features, the REM sleep behavior disorder-neurodegenerative disease association, evolving concepts, controversies, and future directions. *Ann N Y Acad Sci*. 2010 Jan;1184:15-54.
2. **Boeve BF**. Predicting the future in idiopathic rapid-eye movement sleep behaviour disorder. *Lancet Neurol*. 2010 Nov;9(11):1040-2.
3. **Boeve BF**, Silber MH, Ferman TJ, Lin SC, Benarroch EE, Schmeichel AM, Ahlskog JE, Caselli RJ, Jacobson S, Sabbagh M, Adler C, Woodruff B, Beach TG, Iranzo A, Gelpi E, Santamaria J, Tolosa E, Singer C, Mash DC, Luca C, Arnulf I, Duyckaerts C, Schenck CH, Mahowald MW, Dauvilliers Y, Graff-Radford NR, Wszolek ZK, Parisi JE, Dugger B, Murray ME, Dickson DW. Clinicopathologic correlations in 172 cases of rapid eye movement sleep behavior disorder with or without a coexisting neurologic disorder. *Sleep Med.* 2013 Aug;14(8):754-62.
4. **Boeve BF**. Idiopathic REM sleep behaviour disorder in the development of Parkinson's disease. *Lancet Neurol.* 2013 May;12(5):469-82.

4. Characterization of familial neurodegenerative disorders

I have been involved in the identification and characterization of kindreds with familial neurodegenerative disorders since 1996 (over 50 publications). This work has been particularly productive in familial FTLD, in which some of the kindreds that my colleagues and I have evaluated and followed proved to be some of the key index families in the identification of mutations in progranulin (*PGRN*), and later, the hexanucleotide expansion in chromosome 9 open reading frame 72 (*C9ORF72*). I have also been following numerous members of kindreds with mutations in the microtubule associated protein tau (*MAPT*), with many publications emanating from this work. This work in familial FTLD led to the eventual development (I am co-PI) of the Longitudinal Evaluation of Familial Frontotemporal Dementia Subjects (LEFFTDS) protocol (U01 AG045390). My work also contributed to the identification of a novel octapeptide expansion in the gene encoding prion protein (PRNP) in one family. My colleagues at Mayo Clinic and I have also recruited and characterized >100 kindreds who are participating in the Late Onset Alzheimer's Disease Family Study.

1. Baker M, Mackenzie IR Pickering-Brown SM, Gass J, Rademakers R, Lindholm C, Snowden J, Adamson J, Sadovnick AD, Rollinson S, Cannon A, Dwosh E, Neary D, Melquist S, Richardson A, Dickson D, Berger Z, Ericksen J, Robinson T, Zehr C, Dickey CA, Crook R, McGowan E, Mann D,.**Boeve B**, Feldman H, Hutton M. Mutations in progranulin cause tau-negative frontotemporal dementia linked to chromosome 17. *Nature 2006*;442:916-919.
2. Kelley BJ, Haidar W, **Boeve BF**, Baker M, Graff-Radford NR, Krefft T, Frank AR, Jack CR Jr, Shiung M, Knopman DS, Josephs KA, Parashos SA, Rademakers R, Hutton M, Pickering-Brown S, Adamson J, Kuntz KM, Dickson DW, Parisi JE, Smith GE, Ivnik RJ, Petersen RC. Prominent phenotypic variability associated with mutations in Progranulin. Neurobiol Aging 2009 May;30(5):739-51.
3. Dejesus-Hernandez M, Mackenzie IR, **Boeve BF**, Boxer AL, Baker M, Rutherford NJ, Nicholson AM, Finch NA, Flynn H, Adamson J, Kouri N, Wojtas A, Sengdy P, Hsiung GY, Karydas A, Seeley WW, Josephs KA, Coppola G, Geschwind DH, Wszolek ZK, Feldman H, Knopman DS, Petersen RC, Miller BL, Dickson DW, Boylan KB, Graff-Radford NR, Rademakers R. Expanded GGGGCC Hexanucleotide Repeat in Noncoding Region of C9ORF72 Causes Chromosome 9p-Linked FTD and ALS. *Neuron.* 2011 Oct 20;72(2):245-56.
4. **Boeve BF**, Boylan KB, Graff-Radford NR, Dejesus-Hernandez M, Knopman DS, Pedraza O, Vemuri P, Jones D, Lowe V, Murray ME, Dickson DW, Josephs KA, Rush BK, Machulda MM, Fields JA, Ferman TJ, Baker M, Rutherford NJ, Adamson J, Wszolek ZK, Adeli A, Savica R, Boot B, Kuntz KM, Gavrilova R, Reeves A, Whitwell J, Kantarci K, Jack CR Jr, Parisi JE, Lucas JA, Petersen RC, Rademakers R. Characterization of frontotemporal dementia and/or amyotrophic lateral sclerosis associated with the GGGGCC repeat expansion in *C9ORF72*. *Brain.* 2012 Mar;135(Pt 3):765-83.

5. Characterization of mild cognitive impairment

I have been involved in the identification and characterization of patients with mild cognitive impairment (MCI) since the 1990s (over 15 publications). This work includes patients with MCI in the oldest old, within the MCI to AD evolution, and within the MCI to DLB evolution.

1. **Boeve B**, McCormick J, Smith G, Ferman T, Rummans T, Carpenter T, Ivnik R, Kokmen E, Tangalos E, Edland S, Knopman D, Petersen R. Mild cognitive impairment in the oldest old Neurology 2003;60:477-480.
2. Molano J, **Boeve B**, Ferman T, Smith G, Parisi J, Dickson D, Knopman D, Graff-Radford N, Geda Y, Lucas J, Kantarci K, Shiung M, Jack C, Silber M, Pankratz VS, Petersen R. Mild cognitive impairment associated with limbic and neocortical Lewy body disease: a clinicopathological study. *Brain.* 2010 Feb;133(Pt 2):540-56.
3. Ferman TJ, Smith GE, Kantarci K, **Boeve BF**, Pankratz VS, Dickson DW, Graff-Radford NR, Wszolek Z, Van Gerpen J, Uitti R, Pedraza O, Murray ME, Aakre J, Parisi J, Knopman DS, Petersen RC. Nonamnestic mild cognitive impairment progresses to dementia with Lewy bodies. *Neurology*. 2013 Nov 8.

Complete List of Published Work in MyBibliography:
http://www.ncbi.nlm.nih.gov/myncbi/collections/bibliography/40269533/

D. Research Support

U01 AG045390 (Boeve, BF/Rosen H) 09/30/14 to 05/31/19
National Institute on Aging/NINDS
Longitudinal Evaluation of Familial Frontotemporal Dementia Subjects (LEFFTDS)

The major goals of this project evaluate subjects (symptomatic and asymptomatic) in families with known mutations in the genes encoding microtubule associated protein tau (MAPT), progranulin (PGRN) and chromosome 9 open reading frame 72 (C9ORF72) with serial clinical, neuropsychologic, biofluid and MRI studies, and use these findings to design future disease-modifying therapeutic trials.

U54 NS092089 (Boxer, A) 07/01/14 to 06/30/19
National Institute of Neurological Disorders and Stroke/National Center for Advancing Translational Studies
Advancement of Research and Treatment in Frontotemporal Lobar Degeneration (ARTFL)

The goal of this project is to establish a rare disease clinical research network for FTLD.

P50 AG016574 (Petersen, RC) 05/01/14 to 04/30/19
National Institute on Aging
Mayo Alzheimer's Disease Research Center (Core B)

The major goals of this project are to recruit and evaluate patients with mild cognitive impairment, Alzheimer's disease and other dementing illnesses for use in a variety of research projects.

U01 AG006786 (Petersen, RC) 09/01/14 to 08/31/19
National Institute on Aging
Mayo Alzheimer's Disease Patient Registry

The major goals of this project are to recruit and evaluate community subjects for the study of cognitive changes in normal aging, mild cognitive impairment, and dementia.

R01 AG041797 (Mayeux, R) 04/01/13 to 03/30/18
National Institute on Aging
Epidemiology of Familial Late Onset Alzheimer's Disease

The major goals of this project are to recruit and obtain blood samples on patients with Alzheimer's disease and their normal and affected relatives and longitudinally follow subjects to study the epidemiology of familial late onset Alzheimer's disease.

Mangurian Foundation (Dickson, D) 01/01/11 to 12/31/16
Lewy Body Dementia Research

The major goals of this project are to evaluate patients with dementia with Lewy bodies and recruit and follow them longitudinally in any of several aging and dementia research programs.

11-DAT-003-1 (Boeve, B) 03/01/11 to 12/31/16
GE Healthcare
DaTSCAN Imaging in Aging and Neurodegenerative Disease

The goal of this study is to investigate safety and efficacy of DaTSCAN [Ioflupane (^{123}I)] in patients of normal aging, REM sleep behavior disorder and neurodegenerative disease.

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. DO NOT EXCEED FIVE PAGES.

NAME: Mielke, Michelle M.

eRA COMMONS USER NAME (credential, e.g., agency login): mmielke1

POSITION TITLE: Associate Professor of Epidemiology and Neurology

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
University of Pittsburgh, Pittsburgh, PA	B.S.	05/1999	Neuroscience
Johns Hopkins Bloomberg School of Public Health, Baltimore, MD	Ph.D.	05/2004	Neuroepidemiology
Johns Hopkins Bloomberg School of Public Health, Baltimore, MD	Post-doc	06/2005	Epidemiology of Aging
Johns Hopkins University School of Medicine, Baltimore, MD	Post-doc	06/2006	Neuropsychiatry

A. Personal Statement

I have the expertise, leadership and motivation necessary to successfully contribute to the proposed work. I have been trained in neuroscience and neuroepidemiology and have used this training to position myself as a translational epidemiologist examining blood-based lipid, CSF, and neuroimaging biomarkers of neurodegenerative diseases. I am the PI of several NIH-funded clinical- and epidemiological-based grants examining sphingolipids for the development and progression of Alzheimer's disease (AD), Parkinson's disease (PD), and Lewy Body Dementia (DLB). Our group was the first to publish on plasma ceramides and glucosylceramides as potential blood-based biomarkers of cognitive impairment in PD. Thus, this proposal is a natural extension of our work. I will contribute to the proposed application by lending my expertise in ceramide and glucosylceramide biomarkers for PD and DLB. I look forward to working with Dr. Graff-Radford and colleagues on this important proposal.

B. Positions and Honors

Positions and Employment

2006-2007 Instructor, Department of Psychiatry, Johns Hopkins University School of Medicine; Joint Appointment in the Department of Mental Health, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD
2007-2011 Assistant Professor, Department of Psychiatry, Johns Hopkins University School of Medicine, Baltimore, MD
2011-1012 Assistant Professor, Section of Epidemiology, Department of Health Sciences Research, Mayo Clinic College of Medicine, Rochester, MN
2011-present Adjunct Assistant Professor, Department of Psychiatry, Johns Hopkins University School of Medicine, Baltimore, MD
2012-present Associate Professor, Section of Epidemiology, Department of Health Sciences Research, Mayo Clinic College of Medicine, Rochester, MN
2013-present Associate Professor, Department of Neurology, Mayo Clinic College of Medicine, Rochester, MN

Other Experience and Professional Memberships

2009 Ad-hoc Member, CSR Special Emphasis Panels ZRG1 BDCN-T, ZRG1 PSE-C, ZRG1 PSE-J
2010 Ad-hoc Member, CSR Neurological, Aging and Musculoskeletal Epidemiology (NAME) Study Section

2011-present Member, Peripheral and Central Nervous System FDA Panel
2011-present Associate Editor, Journal of Alzheimer's Disease
2012-present Associate Editor, Alzheimer's and Dementia: The Journal of the Alzheimer's Association
2012 Guest Associate Editor, International Journal of Alzheimer's Disease
2013 Guest Associate Editor, Journal of Aging Research
2013 Panel Member, Geoffrey Beene Global NeuroDiscovery Challenge
2014 Ad-hoc Member, Human Disorder Epidemiology, R15 Study Section (ZRG1 PSE-T)
2014-present Member, CSR Neurological, Aging and Musculoskeletal Epidemiology (NAME) Study Section
2015 Reviewer, EU Joint Program – Neurodegenerative Disease Research
2015 Member, Alzheimer's Association Task Force on Gender Vulnerabilities
2015-present Member, NIH Computerized/Remote Cognitive Assessment Committee

Honors

1997 University of Pittsburgh travel grant to present at the Society for Neuroscience Conference
1997-1999 Golden Key National Honor Society
2000-2004 National Institute of Mental Health Pre-doctoral Fellow
2005 Harold and Sylvia Halpert Endowment Award, Department of Mental Health, Johns Hopkins Bloomberg School of Public Health
2005 Vascular, Behavioural and Cognitive Disorders Conference International Travel Award
2005 Lydia Gillespie Clinical and Research Post-doctoral Fellowship in Psychiatry
2006 National Institute of Health Loan Repayment Program Recipient
2007 Fellow, 13th NIMH Summer Research Institute in Geriatric Psychiatry
2007 International College of Geriatric Psychoneuropharmacology (ICGP) Junior Investigator Award
2010 Scholar, NIMH Advanced Research Institute in Geriatric Psychiatry

C. Contribution to Science

1. **Identification of blood-based biomarkers for Alzheimer's disease (AD), Lewy Body Dementia (DLB), and Parkinson's disease (PD).** From an epidemiological perspective, the identification of a blood-based biomarker for AD would be much less invasive and costly and more feasible for repeated measures than a CSF- or neuroimaging-based biomarker. Therefore, I have worked to translate work at the basic science and animal level to identify and develop blood-based biomarkers for the diagnoses and prognoses of AD, DLB, and PD. Much of my work has focused on sphingolipids, which have been associated with AD, DLB, and PD pathology at the animal and cellular levels. I led several studies translating this work to humans. For example, we reported that high blood ceramide levels predicted cognitive impairment and AD among CN individuals; memory decline and hippocampal volume loss among amnestic MCI patients; and faster rates of cognitive decline among AD patients. We also reported that plasma ceramides and glucosylceramides differed by cognitive impairment in PD patients. Interestingly, different parts of the sphingolipid pathway may result in susceptibility for specific neurodegenerative disease. This work is leading to new ways of predicting rate of pathological progression and cognitive decline across neurodegenerative diseases and to the development of new treatment targets and biomarkers for AD.
    a. **Mielke MM**, Maetzler W, Haughey NJ, Bandaru VVR, Savica R, Deuschle C, Gasser T, Hauser AK, Gräber-Sultan S, Schleicher E, Berg D, Liepelt-Scarfone I. Plasma ceramide and glucosylceramide metabolism is altered in sporadic Parkinson's disease and associated with cognitive impairment: a pilot study. PLoS ONE 2013 Sept;8(9):e73094. PMCID: PMC3776817
    b. Mielke, M.M., Bandaru, V.V.R., Haughey, N.J., Rabins, P.V., Lyketsos, C.G., Carlson, M.C. (2010). Serum sphingomyelins and ceramides are early predictors of memory impairment. Neurobiol Aging, 31(1), 17-24. PMCID: PMC2783210
    c. Mielke, M.M., Haughey, N.J., Bandaru, V.V.R., Weinberg, D.D., Darby, E., Zaidi, N., Pavlik, V., Doody, R.S., & Lyketsos, C.G. (2011). Plasma sphingomyelins are associated with cognitive progression in Alzheimer's disease. J Alzheimers Dis 27(2), 259-269. PMCID: PMC3218198
    d. Mielke, M.M., Bandaru, V.V.R., Haughey, N.J., Xia, J., Fried, L.P., Yasar, S., Albert, M., Varma, V., Harris, G., Schneider, E.B., Rabins, P.V., Bandeen-Roche, K., Lyketsos, C.G., & Carlson, M.C. (2012). Serum ceramides increase the risk of Alzheimer disease: the Women's Health and Aging Study II. Neurology 79(7), 633-641. PMCID: PMC3414665

2. **Focus on identification of early brain changes in the preclinical and early clinical stages of AD.** I have both led and contributed to multiple studies focused on understanding brain changes in the pre-clinical and early clinical stages of AD. Using diffusion tensor imaging, our group was one of the first to longitudinally characterize change in brain white matter integrity among individuals who were cognitively normal (CN), had mild cognitive impairment (MCI), or AD. I have also contributed to the estimates of age-specific population frequencies of amyloid and neurodegeneration in CN individuals and to the examination of the temporality of changes in amyloid and neurodegeneration. This work is important for understanding and identifying the early brain changes associated with AD for use in identifying individuals at greatest risk and for developing sensitive outcomes for therapeutic trials.
    a. Mielke, M.M., Kozauer, N.A., Chan, K.C.G., George, M., Toroney, J., Zerrate, M., Bandeen-Roche, K., Wang, M.-C., vanZijl, P., Pekar, J.J., Mori, S., Lyketsos, C.G., & Albert, M. (2009). Regionally-specific diffusion tensor imaging in mild cognitive impairment and Alzheimer's disease. NeuroImage, 46(1), 47-55. PMCID: PMC2688089
    b. Mielke, M.M., Okonkwo, O.C., Oishi, K., Mori, S., Tighe, S., Miller, M.I., Ceritoglu, C., Brown, T., Albert, M., & Lyketsos, C.G. (2012). Fornix integrity and hippocampal volume predict memory decline and progression to Alzheimer's disease. Alzheimer's Dement, 8(2), 105-113. PMCID: PMC3305232
    c. Nowrangi, M.A., Lyketsos, C.G., Leoutsakos, J.-M.S., Oishi, K., Albert, M., Mori, S., & Mielke, M.M. (2013). Longitudinal, region-specific course of diffusion tensor imaging measures in mild cognitive impairment and Alzheimer's disease. Alzheimer's Dement, 9(5), 519-528. PMCID: PMC3639296
    d. Jack, C.R. Jr, Wiste, H.J., Weigand, S.D., Rocca, W.A., Knopman, D.S., Mielke, M.M., Lowe, V.J., Senjem, M.L., Gunter, J.L., Preboske, G.M., Pankratz, V.S., Vemuri, P., & Petersen, R.C. (2014). Age-specific population frequencies of cerebral β-amyloidosis and neurodegeneration among people with normal cognitive function aged 50-89 years: a cross-sectional study. Lancet Neurol, 13(10), 997-1005. PMCID: PMC4324499

3. **Focus on sex and gender differences for risk of dementia and cardiovascular disease.** For most diseases, the overall risk of a specific disease, rate of progression, and treatment response vary by sex. However, there is a paucity of studies focused on sex and gender differences for disease risk; most studies have simply controlled for sex. I have collaborated on or led several studies focused on understanding the sex-specific risk of pregnancy and menopause for future cardiovascular disease, and sex and gender differences in the risk of Alzheimer's disease. With the increasing focus on personalized medicine, this work provides a foundation for understanding individualized disease risk.
    a. Miller, V.M., Garovic, V.D., Kantarci, K., Barnes, J.N., Jayachandran, M., Mielke, M.M., Joyner, M.J., Shuster, L.T., & Rocca, W.A. (2013). Sex-specific risk of cardiovascular disease and cognitive decline: pregnancy and menopause. Biol Sex Differ, 4(1), 6. PMCID: PMC3623746
    b. Mielke, M.M., Vemuri, P., & Rocca, W.A. (2014). Clinical epidemiology of Alzheimer's disease: assessing sex and gender differences. Clin Epidemiol, 6, 37-48. PMCID: PMC3891487
    c. Rocca, W.A., Mielke, M.M., Vemuri, P., & Miller, V.M. (2014). Sex and gender differences in the causes of dementia: a narrative review. Maturitas 79(2), 196-201. PMCID: PMC4169309
    d. Roberts, R.O., Geda, Y.E., Knopman, D.S., Cha, R.H., Pankratz, V.S., Boeve, B.F., Tangalos, E.G., Ivnik, R.J., Mielke, M.M., & Petersen, R.C. (2013). Cardiac disease associated with increased risk of nonamnestic mild cognitive impairment: stronger effect on women. JAMA Neurol, 70(3), 374-382. PMCID: PMC3734560

4. **Focus on vascular risk factors for AD.** I have led several studies examining the importance and timing (mid-life vs. late-life) of vascular risk factors for MCI and AD using large epidemiological studies across the United States and in Sweden. We showed that the relationship between plasma cholesterol and risk of dementia differed depending on when the risk factor was measured in relation to the onset of dementia. Specifically, high mid-life cholesterol and low late-life cholesterol (or decline in cholesterol from mid- to late-life) was associated with an increased risk of dementia. This indicates that vascular risk factors are important to treat in mid-life to prevent or delay the onset of dementia. Further, lowering of cholesterol (or blood pressure) from mid- to late-life may be an indicator of underlying brain pathology and risk of dementia. Additional work also demonstrated that vascular risk factors and diseases are associated with faster rates of decline after a diagnosis of AD. This work was significant for demonstrating the importance of treating vascular comorbidities in persons with AD.

a. Mielke, M.M., Zandi, P.P., Sjögren, M., Gustafson, D., Östling, S., Steen, B., & Skoog, I. (2005). High total cholesterol levels in late life associated with a reduced risk of dementia. Neurology, 64(10), 1689-1695.
b. Mielke, M.M., Rosenberg, P.B., Tschanz, J., Cook, L., Corcoran, C., Hayden, K.M., Norton, M., Rabins, P.V., Green, R.C., Welsh-Bohmer, K.A., Breitner, J.C.S., Munger, R., & Lyketsos, C.G. (2007). Vascular factors predict rate of progression in Alzheimer's disease. Neurology 69(19), 1850-1858.
c. Mielke, M.M., Zandi, P.P., Shao, H., Waern, M., Östling, S., Guo, X., Björkelund, C., Lissner, L., Skoog, I., & Gustafson, D.R. (2010). The 32-year relationship between cholesterol and dementia from midlife to late life. Neurology 75(21), 1888-1895. PMCID: PMC2995387
d. Roberts, R.O., Knopman, D.S., Przybelski, S.A., Mielke, M.M., Kantarci, K., Preboske, G.M., Senjem, M.L., Pankratz, V.S., Geda, Y.E., Boeve, B.F., Ivnik, R.J., Rocca, W.A., Petersen, R.C., & Jack, C.R. Jr. (2014). Association of type 2 diabetes with brain atrophy and cognitive impairment. Neurology 82(13), 1132-1141. PMCID: PMC3966799

Complete List of Published Work in My Bibliography:
http://www.ncbi.nlm.nih.gov/sites/myncbi/michelle.mielke.1/bibliography/41127186/public/?sort=date&direction=ascending

D. Research Support

Ongoing Research Support

1 R01 AG 049704-01 Mielke (PI) 09/01/2015 – 04/30/2019
NIH/NIA
Sphingolipids and Inflammation in the Development and Progression of Alzheimer's
The overarching goal of this project is to determine the temporal relationship between plasma and CSF sphingolipids (e.g., ceramides, sphingomyelins), and measures of Aβ pathology, neurodegeneration, and cognitive decline. We will also determine whether inflammatory processes (e.g., TNF-α and IL-6) modify these associations.
Role: Principal Investigator

FP00074480 Mielke (PI) 01/01/14-06/30/15, NCE
Michael J. Fox Foundation for Parkinson's Research
Assessment of Plasma Glucosylceramides and Ceramides as Biomarkers of Cognitive Impairment in Parkinson's Disease
This study aims to determine whether plasma ceramide and glucosylceramide levels are associated with cognitive impairment in patients with Parkinson's disease (PD), including those with and without *GBA* mutations, and predict rate of cognitive decline. We will use blood and data already collected from 500 PD patients enrolled in the Dempark/Landscape study and follow-up for up to 3 years. This project will determine the utility of plasma ceramide and glucosylceramide as blood-based cognitive biomarkers in PD.
Role: Principal Investigator

U01 AG06786-29 Petersen (PI) 07/01/14-06/30/19
Alzheimer's Disease Patient Registry
The overall goal of this revision is to use the infrastructure of the Mayo Clinic Study of Aging (MCSA), with population-based recruitment of Olmsted County, MN residents aged 70+, to establish a younger population-based sample of persons aged 50-69. We will examine risk factors of mild cognitive impairment (MCI) and dementia, determine the prevalence of abnormal biomarkers of Alzheimer's disease pathophysiology, develop risk models of MCI and AD, and assess the sensitivity of a computerized cognitive battery to early cognitive change.
Role: Co-Investigator

2P30 MH75673-9 Mielke (PI) 07/01/11-06/30/16
Center for Novel Therapeutics for HIV-Associated Cognitive Disorders
The primary goals of the Surrogate Marker / Pharmacokinetic Core will be to: 1) Assist in the development and monitoring of surrogate markers for HIV-associated neurocognitive disorders (HAND). 2) To provide mentorship and consultation for Neuro-AIDS researchers in the development of clinically useful surrogate

markers for HAND and to validate these as predictive and associative markers for cognitive impairment and as surrogate markers for therapeutic effectiveness.
Role: Principal Investigator of Sub-contract

AZ140069-1 Brown/Mielke (co-PI) 09/15/2015 – 09/14/2018
Department of Defense
Understanding the Connection Between Traumatic Brain Injury and Alzheimer's Disease: A Population-based Study
Most studies of traumatic brain injury have been conducted on select populations. This study will ascertain the incidence of TBI in Olmsted County, Minnesota between 1985 and 1999 using the Rochester Epidemiology Medical Records linkage system. We will then longitudinally determine whether TBI, including number of events and severity, is associated with subsequent risk of Alzheimer's disease and other neurodegeneration conditions.

P50 AG44170-3 Miller (PI) 09/01/12-08/31/17
Sex-specific Risk for Vascular Dysfunction and Cognitive Decline. Project 1 – Hypertension in Pregnancy and Future Cardiovascular Disease
This program-project application seeks to develop a Specialized Center for Research on Sex Differences at Mayo Clinic. Dr. Mielke is involved in Project 1 of the proposed center. The overarching hypothesis of Project 1 is that a history of hypertensive pregnancy disorders, in general, and preeclampsia, in particular, are risk factors for mortality (all-cause and cardiovascular), future CVD, and cognitive impairment. We will test this hypothesis using the unique population-based records-linkage system of the Rochester Epidemiology Project (REP).
Role: Co-Investigator

Completed Research Support (within last 3 years)

FP00082085 Mielke (PI) 03/01/2015-8/31/2015
Michael J. Fox Foundation for Parkinson's Research
Comparison of Pre- and Post-mortem CSF Levels of Proteins and Lipids
Few studies have utilized post-mortem CSF samples, for a variety of reasons. This pilot study will examine the correlation between pre- and post-mortem CSF levels of alpha-synuclein, amyloid-beta, tau, and sphingolipids, which are all biomarkers of interest for PD.
Role: Principal Investigator

P50 AG16574 Mielke (PI of pilot project) 05/01/2014-04/30/2015
Change in Plasma Ceramide and Glucosylceramides with the Clinical Phenotype of Lewy Body Dementia
This study aimed: 1) To determine whether plasma ceramides and glucosylceramides differed by stage of DLB (iRBD, RBD-MCI, DLB); 2) To examine the cross-sectional association between plasma ceramides and glucosylceramides and neuroimaging parameters associated with DLB subjects; and 3) To examine whether plasma ceramides and glucosylceramides changed with disease progression.

U01 AG037526-5 Mielke (PI) 09/01/11-05/31/15
Longitudinal Study of Lipids and APOE in the Development of AD and AD Pathology
The overall aim of the proposed study is to examine, in the 30-year follow-up of participants in the Baltimore Longitudinal Study of Aging, whether peripheral lipids (sphingolipids, fatty acids, cholesterol and cholesterol esters) modify the association between ApoE and clinical onset of MCI or AD.
Role: Principal Investigator

Driskill Foundation-1 Petersen/Mielke (PIs) 04/01/12-03/31/15
Walter S. and Lucienne Driskill Foundation
Computerized Assessment and Neuroimaging in Study of Aging Younger Cohort
The major goal of this project was to examine the role of a computerized instrument (CogState) as a first-line screen to identify persons who should have more extensive cognitive testing using standard pencil-and-paper neuropsychological tests and more invasive and expensive Alzheimer Disease biomarker evaluations.
Role: Co-Program Director/Principal Investigator

RESOURCES

Follow the 398 application instructions in Part I, 4.7 Resources.

At Mayo Clinic Jacksonville, there are 369 full-time staff in medicine, surgery, and associated sciences; 4,547 allied health staff; and 334 residents, fellows, students, and other trainees. The staff attends over 91,000 patients each year. Patients also come from all over the world, although most are from the Southeastern United States. In April 2008, Mayo Clinic opened its new hospital 214-bed, 650,000 square foot campus on the San Pablo Road campus.

The Department of Neurology at Mayo Clinic Jacksonville includes 20 neurologists with permanent appointments to the medical staff. In addition, the Adult Neurology Residency Program has 11 residents and 2 fellows currently in training.

Each of the clinicians has a personal office equipped with personal computer, widescreen monitor, and telephone. Each clinician has his or her own examination room equipped with landline, computer, ophthalmoscope, and otoscope. In the Cannaday Building, there are 19 examination rooms shared by 18 neurologists. Each clinician has secretarial support. Each secretary has her own cubical equipped with landline, computer, printer/fax machine. The Department has its own “front desk” where the patients register and are directed to the examination rooms. Four attendants staff the front desk at the MCF. The front desk personnel also include 6 other attendants whose functions relate to scheduling the ordered tests and consultations. There are two vitals signs stations located at the front of the hallways. There is a sterile procedure room for performing lumbar punctures, processing blood samples, and performing electodiagnostic testing and injection therapies like botulinum toxin. There is also a telemedicine office that allows for timely CCTV assessment of patients with acute stroke-like presentations at remote emergency departments.

The Department of Neurology has an ACGME-accredited Neurology Residency, founded in 2002, which matriculates 4 residents per year. The Department of Neurosurgery has an ACGME-accredited Neurosurgery Residency, founded in 2012, which matriculates one resident per year. Additionally, there are fellowships in Behavioral Neurology, Hospitalist Neurology, and Neurocritical care.

Animal:

Not applicable

Computer:

The PI and all co-investigators have PCs fully integrated with the Mayo network that provide flexible access to all files and email from home or office.

Office:

Office space for Jacksonville ADRC clinical investigators and staff is located on the second floor of the Cannaday Building. This area includes 12 work stations for research coordinators and nurses, two examination rooms, two testing rooms, one Phlebotomy room and offices for the project manager and principal investigator. Dr. Graff-Radford has a 100 sq ft office on the third floor of the Birdsall Building with 400 sq. ft. of adjacent space with networked computers, fax machine, copier and filing areas.

Other:

Video Communication System. The telecommunication system affords us an opportunity to meet in a videoconference setting for administrative, clinical and educational purposes. The Mayo Video Communication System provides service via the asynchronous transfer mode. The system uses five T-1 lines for videoconferencing. The system provides full motion video capabilities. In addition, there are nine T-1 lines for data transmission which provide the infrastructure for our database system in Rochester and Jacksonville. There are five rooms in Jacksonville capable of two-way communications. The system is

available 24 hours a day seven days a week and can accommodate five simultaneous conferences using five channels available between Rochester and Jacksonville. The system is provided by the Mayo Foundation at no charge to this grant. Meetings will be held monthly using this system.

FACILITIES AND OTHER RESOURCES

The Mayo Alzheimer Disease Research Center (ADRC) research program began operating as a P30 in September 1990 and was upgraded to a P50 in May 1999. Mayo Clinic is the first and largest integrated, not-for-profit medical group practice in the world. More than 4,000 physicians and scientists and 53,600 allied health staff provide innovative health care across Mayo campuses in Rochester, Minn., Jacksonville, Fla., Scottsdale, Ariz., and 70 other communities in Iowa, Minnesota, Georgia and Wisconsin. Mayo Clinic Rochester treats over 340,000 patients each year, comprising 1.5 million patient visits. There are 3,400 residents, fellows, and students enrolled in the Mayo Medical School, Mayo Graduate School, Mayo School of Graduate Medical Education, and Mayo School of Health Sciences. Mayo Clinic doctors work with nurses, scientists and patients to direct studies in nearly every field of medicine. They conduct basic, translational, clinical, and population studies throughout the organization. Mayo employs 3,330 research personnel working with 8,968 research studies. 11,000 patients participated in Mayo clinical trials in 2012.

OFFICE

Office space for Rochester ADRC investigators and staff (Administrative Core, Clinical Core, Outreach, Recruitment, and Education Core) is located at the Northwest Clinic building in Rochester, MN. This facility (approximately 6,300 square feet) contains office space for 2 secretaries, 4 RN study coordinators, 10 clinical research coordinators, 6 associate clinical research coordinators, 1 education coordinator, 8 psychometrists, 1 data entry clerk, 2 program managers, 7 MD/PhD level staff, patient examination rooms, a lobby, a conference room, and space for maintaining records. A laboratory with phlebotomy services, a pharmacy, and a family medicine/internal medicine clinic (with equipment and staff for emergencies should they ever be necessary) are all adjacent to the ADRC in the Northwest Clinic Building. The investigators also have office on the downtown Mayo campus (less than five miles away from the ADRC). All offices at the ADRC and downtown Mayo campus have telephones and computer workstations interconnected within the Mayo network, with electronic access to resources in Rochester, MN; Jacksonville, FL; Scottsdale, AZ; and the Mayo Health System. The Rochester Data Management and Statistical Core personnel have designated office space in the Harwick Building on the downtown Mayo Rochester campus with the Department of Health Sciences Research (Core leader, Dr. Walter Kremers, and data analysts, statisticians). Office space for the Rochester NP Core Leader, Dr. Joseph Parisi, is located on the 11th floor of the Hilton Building with a double-headed Olympus BX50 microscope. In an adjacent work are there is a 7-headed teaching microscope. A separate conference room has a 9-headed teaching microscope that also has a videocamera and a projection monitor.

CLINICAL

The Department of Neurology at Mayo Clinic Rochester includes 80 neurologists with permanent appointments to the medical staff. In addition, there are 28 neurology residents, and 20 post-graduate neurology fellows. There are 12 neurology divisions, many (including the Behavioral Neurology Division) integrating subspecialty interests and activities across three Mayo sites (Mayo Clinic Rochester, Jacksonville, and Scottsdale). The Department has several clinical and research laboratories. The Mayo Department of Neurology has a large clinical practice. It is estimated that of all Mayo Clinic patient registrations, approximately one quarter, have a neurology contact. This rich patient resource permits a broad and comprehensive range of clinical, educational, and research activities throughout the Department.

Program Director/Principal Investigator (Last, First, Middle): Petersen, Ronald C

MAYO CLINIC JACKSONVILLE CHECKLIST

TYPE OF APPLICATION *(Check all that apply.)*

☒ NEW application. *(This application is being submitted to the PHS for the first time.)*

☐ RESUBMISSION of application number: _____
(This application replaces a prior unfunded version of a new, renewal, or revision application.)

☐ RENEWAL of grant number: _____
(This application is to extend a funded grant beyond its current project period.)

☐ REVISION to grant number: _____
(This application is for additional funds to supplement a currently funded grant.)

☐ CHANGE of program director/principal investigator.

Name of former program director/principal investigator: _____

☐ CHANGE of Grantee Institution. Name of former institution: _____

☐ FOREIGN application ☐ Domestic Grant with foreign involvement List Country(ies) Involved:

INVENTIONS AND PATENTS *(Renewal appl. only)* ☐ No ☐ Yes

If "Yes," ☐ Previously reported ☐ Not previously reported

1. PROGRAM INCOME ***(See instructions.)***
All applications must indicate whether program income is anticipated during the period(s) for which grant support is request. If program income is anticipated, use the format below to reflect the amount and source(s).

Budget Period	Anticipated Amount	Source(s)

2. ASSURANCES/CERTIFICATIONS ***(See instructions.)***
In signing the application Face Page, the authorized organizational representative agrees to comply with the policies, assurances and/or certifications listed in the application instructions when applicable. Descriptions of individual assurances/certifications are provided in Part III and listed in Part I, 4.1 under Item 14. If unable to certify compliance, where applicable, provide an explanation and place it after this page.

3. FACILITIES AND ADMINSTRATIVE COSTS (F&A)/ INDIRECT COSTS. See specific instructions.

☒ DHHS Agreement dated: 1/8/2014 ☐ No Facilities And Administrative Costs Requested.

☐ DHHS Agreement being negotiated with _____ Regional Office.

☐ No DHHS Agreement, but rate established with _____ Date _____

CALCULATION* *(The entire grant application, including the Checklist, will be reproduced and provided to peer reviewers as confidential information.)*

a. Initial budget period:	Amount of base $	14,157	x Rate applied	56.50%	% = F&A costs	$	7,999
b. 02 year	Amount of base $	13,772	x Rate applied	56.50%	% = F&A costs	$	7,781
c. 03 year	Amount of base $		x Rate applied	0.00%	% = F&A costs	$	
d. 04 year	Amount of base $		x Rate applied	0.00%	% = F&A costs	$	
e. 05 year	Amount of base $		x Rate applied	0.00%	% = F&A costs	$	
					TOTAL F&A Costs	$	15,780

*Check appropriate box(es):

☐ Salary and wages base ☒ Modified total direct cost base ☐ Other base *(Explain)*

☐ Off-site, other special rate, or more than one rate involved *(Explain)*

Explanation *(Attach separate sheet, if necessary.):*

4. DISCLOSURE PERMISSION STATEMENT: If this application does not result in an award, is the Government permitted to disclose the title of your proposed project, and the name, address, telephone number and e-mail address of the official signing for the applicant organization, to organizations that may be interested in contacting you for further information (e.g., possible collaborations, investment)? ☐ Yes ☐ No

Program Director/Principal Investigator (Last, First, Middle): Petersen, Ronald C

MAYO CLINIC ROCHESTER CHECKLIST

TYPE OF APPLICATION *(Check all that apply.)*

☒ NEW application. *(This application is being submitted to the PHS for the first time.)*

☐ RESUBMISSION of application number: _____
(This application replaces a prior unfunded version of a new, renewal, or revision application.)

☐ RENEWAL of grant number: _____
(This application is to extend a funded grant beyond its current project period.)

☐ REVISION to grant number: _____
(This application is for additional funds to supplement a currently funded grant.)

☐ CHANGE of program director/principal investigator.

Name of former program director/principal investigator: _____

☐ CHANGE of Grantee Institution. Name of former institution: _____

☐ FOREIGN application ☐ Domestic Grant with foreign involvement List Country(ies) Involved:

INVENTIONS AND PATENTS *(Renewal appl. only)* ☐ No ☐ Yes

If "Yes," ☐ Previously reported ☐ Not previously reported

1. PROGRAM INCOME ***(See instructions.)***
All applications must indicate whether program income is anticipated during the period(s) for which grant support is request. If program income is anticipated, use the format below to reflect the amount and source(s).

Budget Period	Anticipated Amount	Source(s)

2. ASSURANCES/CERTIFICATIONS ***(See instructions.)***
In signing the application Face Page, the authorized organizational representative agrees to comply with the policies, assurances and/or certifications listed in the application instructions when applicable. Descriptions of individual assurances/certifications are provided in Part III and listed in Part I, 4.1 under Item 14. If unable to certify compliance, where applicable, provide an explanation and place it after this page.

3. FACILITIES AND ADMINSTRATIVE COSTS (F&A)/ INDIRECT COSTS. See specific instructions.

☒ DHHS Agreement dated: 9/3/2015 ☐ No Facilities And Administrative Costs Requested.

☐ DHHS Agreement being negotiated with _____ Regional Office.

☐ No DHHS Agreement, but rate established with _____ Date _____

CALCULATION* *(The entire grant application, including the Checklist, will be reproduced and provided to peer reviewers as confidential information.)*

a. Initial budget period:	Amount of base $	30,555	x Rate applied	59.00%	% = F&A costs	$	18,027
b. 02 year	Amount of base $	32,605	x Rate applied	59.00%	% = F&A costs	$	19,237
c. 03 year	Amount of base $		x Rate applied	0.00%	% = F&A costs	$	
d. 04 year	Amount of base $		x Rate applied	0.00%	% = F&A costs	$	
e. 05 year	Amount of base $		x Rate applied	0.00%	% = F&A costs	$	
					TOTAL F&A Costs	$	37,264

*Check appropriate box(es):

☐ Salary and wages base ☒ Modified total direct cost base ☐ Other base *(Explain)*

☐ Off-site, other special rate, or more than one rate involved *(Explain)*

Explanation *(Attach separate sheet, if necessary.):*

4. DISCLOSURE PERMISSION STATEMENT: If this application does not result in an award, is the Government permitted to disclose the title of your proposed project, and the name, address, telephone number and e-mail address of the official signing for the applicant organization, to organizations that may be interested in contacting you for further information (e.g., possible collaborations, investment)? ☐ Yes ☐ No

MAYO CLINIC
College of Medicine

200 First Street SW
Rochester, Minnesota 55905
507-284-2511

Ronald C. Petersen, Ph.D., M.D.
Cora Kanow Professor of
Alzheimer's Disease Research
507-538-0487, Fax 507-538-6012

January 15, 2016

Walter A. Kukull, PhD
National Alzheimer's Coordinating Center
University of Washington
4311 11th Ave NE Ste 300
Seattle, WA 98105

Dear Bud:

I am writing to express my support for the collaborative grant application titled "Plasma Biomarkers in Lewy Body Disease," which is being submitted for funding by the National Alzheimer's Coordinating Center.

As the Director of the Mayo ADRC, I am endorsing the participation of our Center in this project under the direction of Neill Graff-Radford.

All key personnel associated with this project at our Center have received appropriate DHHS-approved training in human subjects research.

We are pleased to contribute to an increased understanding of this important topic, and we look forward to participating in a scientifically productive project.

Sincerely,

Ronald C. Petersen, Ph.D., M.D.
Professor of Neurology
Distinguished Mayo Clinic Investigator
Cora Kanow Professor of Alzheimer's Disease Research
Cadieux Director, Mayo Alzheimer's Disease Research Center
Director, Mayo Clinic Study of Aging
Alzheimer's PPRN Principal Investigator

rcp/djc

Form Approved Through 8/31/2015 OMB No. 0925-0001

Department of Health and Human Services
Public Health Services

Grant Application

Do not exceed character length restrictions indicated.

LEAVE BLANK—FOR PHS USE ONLY.		
Type	Activity	Number
Review Group		Formerly
Council/Board (Month, Year)		Date Received

1. TITLE OF PROJECT *(Do not exceed 81 characters, including spaces and punctuation.)*
Plasma biomarkers in Lewy Body Disease

2. RESPONSE TO SPECIFIC REQUEST FOR APPLICATIONS OR PROGRAM ANNOUNCEMENT OR SOLICITATION ☐ NO ☒ YES *(If "Yes," state number and title)*
Number: NACC2016-COLLAB Title: NACC-funded Collaborative Projects, FY2016

3. PROGRAM DIRECTOR/PRINCIPAL INVESTIGATOR

3a. NAME (Last, first, middle)	3b. DEGREE(S)	3h. eRA Commons User Name
O'Bryant, Sid E.	PhD	SOBRYANT79430

3c. POSITION TITLE
Associate Professor

3d. MAILING ADDRESS *(Street, city, state, zip code)*
3500 Camp Bowie Blvd.
Fort Worth, TX 76107-2699

3e. DEPARTMENT, SERVICE, LABORATORY, OR EQUIVALENT
Ctr. for Alzheimer's & Neurodegenerative Disease Research

3f. MAJOR SUBDIVISION
Overall Medical

3g. TELEPHONE AND FAX *(Area code, number and extension)*
TEL: 817-735-2961 FAX: 817-735-0628

E-MAIL ADDRESS:
sid.obryant@unthsc.edu

4. HUMAN SUBJECTS RESEARCH	4a. Research Exempt	If "Yes," Exemption No.
☒ No ☐ Yes	☒ No ☐ Yes	

4b. Federal-Wide Assurance No.	4c. Clinical Trial	4d. NIH-defined Phase III Clinical Trial
FWA00005755	☒ No ☐ Yes	☒ No ☐ Yes

5. VERTEBRATE ANIMALS ☒ No ☐ Yes — 5a. Animal Welfare Assurance No

6. DATES OF PROPOSED PERIOD OF SUPPORT *(month, day, year—MM/DD/YY)*		7. COSTS REQUESTED FOR INITIAL BUDGET PERIOD		8. COSTS REQUESTED FOR PROPOSED PERIOD OF SUPPORT	
From	Through	7a. Direct Costs ($)	7b. Total Costs ($)	8a. Direct Costs ($)	8b. Total Costs ($)
07/01/16	06/30/18	$2,277	$3,324	$37,921	$55,365

9. APPLICANT ORGANIZATION
Name University of North Texas Health Science Center
Address
3500 Camp Bowie Blvd.
Fort Worth, TX 76107-2699

10. TYPE OF ORGANIZATION
Public: → ☐ Federal ☒ State ☐ Local
Private: → ☐ Private Nonprofit
For-profit: → ☐ General ☐ Small Business
☐ Woman-owned ☐ Socially and Economically Disadvantaged

11. ENTITY IDENTIFICATION NUMBER
1-756064033
DUNS NO.110091808 Cong. District TX-012

12. ADMINISTRATIVE OFFICIAL TO BE NOTIFIED IF AWARD IS MADE
Name LeAnn Forsberg
Title AVP. Research Administration
Address 3500 Camp Bowie Blvd.
Fort Worth, TX 76107-2699
Tel: 817-735-5073 FAX: 817-735-0375
E-Mail: ogcmext@unthsc.edu

13. OFFICIAL SIGNING FOR APPLICANT ORGANIZATION
Name LeAnn Forsberg
Title AVP. Research Administration
Address 3500 Camp Bowie Blvd.
Fort Worth, TX 76107-2699
Tel: 817-735-5073 FAX: 817-735-0375
E-Mail:

14. APPLICANT ORGANIZATION CERTIFICATION AND ACCEPTANCE: I certify that the statements herein are true, complete and accurate to the best of my knowledge, and accept the obligation to comply with Public Health Services terms and conditions if a grant is awarded as a result of this application. I am aware that any false, fictitious, or fraudulent statements or claims may subject me to criminal, civil, or administrative penalties.

SIGNATURE OF OFFICIAL NAMED IN 13. *(In ink. "Per" signature not acceptable.)*
LeAnn Forsberg

DATE
1/11/16

Use only if preparing an application with Multiple PDs/PIs. See http://grants.nih.gov/grants/multi_pi/index.htm for details.

Contact Program Director/Principal Investigator (Last, First, Middle): O'Bryant, Sid E.

3. PROGRAM DIRECTOR / PRINCIPAL INVESTIGATOR		
3a. NAME (Last, first, middle)	3b. DEGREE(S)	3h. NIH Commons User Name
3c. POSITION TITLE	3d. MAILING ADDRESS *(Street, city, state, zip code)*	
3e. DEPARTMENT, SERVICE, LABORATORY, OR EQUIVALENT		
3f. MAJOR SUBDIVISION		
3g. TELEPHONE AND FAX *(Area code, number and extension)* TEL: FAX:	E-MAIL ADDRESS:	

3. PROGRAM DIRECTOR / PRINCIPAL INVESTIGATOR		
3a. NAME (Last, first, middle)	3b. DEGREE(S)	3h. NIH Commons User Name
3c. POSITION TITLE	3d. MAILING ADDRESS *(Street, city, state, zip code)*	
3e. DEPARTMENT, SERVICE, LABORATORY, OR EQUIVALENT		
3f. MAJOR SUBDIVISION		
3g. TELEPHONE AND FAX *(Area code, number and extension)* TEL: FAX:	E-MAIL ADDRESS:	

3. PROGRAM DIRECTOR / PRINCIPAL INVESTIGATOR		
3a. NAME (Last, first, middle)	3b. DEGREE(S)	3h. NIH Commons User Name
3c. POSITION TITLE	3d. MAILING ADDRESS *(Street, city, state, zip code)*	
3e. DEPARTMENT, SERVICE, LABORATORY, OR EQUIVALENT		
3f. MAJOR SUBDIVISION		
3g. TELEPHONE AND FAX *(Area code, number and extension)* TEL: FAX:	E-MAIL ADDRESS:	

3. PROGRAM DIRECTOR / PRINCIPAL INVESTIGATOR		
3a. NAME (Last, first, middle)	3b. DEGREE(S)	3h. NIH Commons User Name
3c. POSITION TITLE	3d. MAILING ADDRESS *(Street, city, state, zip code)*	
3e. DEPARTMENT, SERVICE, LABORATORY, OR EQUIVALENT		
3f. MAJOR SUBDIVISION		
3g. TELEPHONE AND FAX *(Area code, number and extension)* TEL: FAX:	E-MAIL ADDRESS:	

Program Director/Principal Investigator (Last, First, Middle): O'Bryant, Sid E.

PROJECT SUMMARY (See instructions):

The purpose of this project is to collect the requisite data and build the necessary collaborative relationships to submit a grant for a large-scale prospective study of the utility of blood-based biomarkers in Lewy Body disease (LBD). The long-term goal of this line of research is the generation of blood-based profiles that have diagnostic, prognostic and theragnostic value in LBD. Given the rapidly growing elderly population, neurodegenerative dementias are a major public health problem. LBD is the 2nd most prevalent neurodegenerative dementia accounting for 15-20% of cases and is often misdiagnosed as Alzheimer's disease (AD). LBD is an α-synuclein disorder that is characterized by Lewy Body and Lewy neurites in specific areas of the brain as well as acetylcholine neuronal degeneration. There is frequent AD and LBD overlap making the differential diagnosis between LBD and AD a significant problem in clinical practice. Additionally, there is an urgent need for methods to predict clinical course in LBD to design trials and monitor interventions. Based on preliminary findings it is our hypothesis that a blood-based biomarker profile can be accurate in detecting and distinguishing LBD from AD and controls. The Specific Aims of this project are as follows: Specific Aim 1 – Replicate our blood-based profile of LBD in a larger sample and Specific Aim 2 – To identify biologically-based subgroups in LBD.

RELEVANCE (See instructions):

Lewy Body disease (LBD) is the second most prevalent neurodegenerative dementia and is often misdiagnosed as Alzheimer's disease (AD). Here we propose to generate a simple blood-test that has utility in detecting LBD as well as identify subgroups of LBD patients that may respond differentially to selective treatments. This line of work can have significant impact on the detection and treatment of LBD.

PROJECT/PERFORMANCE SITE(S) (if additional space is needed, use Project/Performance Site Format Page)

Project/Performance Site Primary Location		
Organizational Name: University of North Texas Health Science Center		
DUNS: 110091808		
Street 1: 3500 Camp Bowie Blvd.	Street 2:	
City: Fort Worth	County: Tarrant	State: TX
Province:	Country: United States of America	Zip/Postal Code: 76107
Project/Performance Site Congressional Districts: TX-012		

Additional Project/Performance Site Location		
Organizational Name:		
DUNS:		
Street 1:	Street 2:	
City:	County:	State:
Province:	Country:	Zip/Postal Code:
Project/Performance Site Congressional Districts:		

SCIENTIFIC/KEY PERSONNEL. See instructions. *Use continuation pages as needed* to provide the required information in the format shown below. Start with Program Director(s)/Principal Investigator(s). List all other key personnel in alphabetical order, last name first.

Name	eRA Commons User Name	Organization	Role on Project
Sid O'Braynt	SOBRYANT79430	UNTHSC	PI
Fan Zhang	fanzhan	UNTHSC	Co-Investigator

OTHER SIGNIFICANT CONTRIBUTORS

Name	Organization	Role on Project

Human Embryonic Stem Cells ☒ **No** ☐ **Yes**

If the proposed project involves human embryonic stem cells, list below the registration number of the specific cell line(s) from the following list: http://stemcells.nih.gov/research/registry/eligibilityCriteria.asp. *Use continuation pages as needed.*

If a specific line cannot be referenced at this time, include a statement that one from the Registry will be used.

Cell Line

Program Director/Principal Investigator (Last, First, Middle): O'Bryant, Sid E.

DETAILED BUDGET FOR INITIAL BUDGET PERIOD
DIRECT COSTS ONLY

FROM 7/1/2016 THROUGH 6/30/2017

List PERSONNEL *(Applicant organization only)*
Use Cal, Acad, or Summer to Enter Months Devoted to Project
Enter Dollar Amounts Requested *(omit cents)* for Salary Requested and Fringe Benefits

NAME	ROLE ON PROJECT	Cal. Mnths	Acad. Mnths	Summer Mnths	INST.BASE SALARY	SALARY REQUESTED	FRINGE BENEFITS	TOTAL
Sid O'Bryant	PD/PI	.12			185,100	1,851	426	2,277
SUBTOTALS →						1,851	426	2,277

CONSULTANT COSTS	
EQUIPMENT *(Itemize)*	
SUPPLIES *(Itemize by category)*	
TRAVEL	
INPATIENT CARE COSTS	
OUTPATIENT CARE COSTS	
ALTERATIONS AND RENOVATIONS *(Itemize by category)*	
OTHER EXPENSES *(Itemize by category)*	

CONSORTIUM/CONTRACTUAL COSTS	DIRECT COSTS	
SUBTOTAL DIRECT COSTS FOR INITIAL BUDGET PERIOD *(Item 7a, Face Page)*		$ 2,277
CONSORTIUM/CONTRACTUAL COSTS	FACILITIES AND ADMINISTRATIVE COSTS	
TOTAL DIRECT COSTS FOR INITIAL BUDGET PERIOD		$ 2,277

BUDGET FOR ENTIRE PROPOSED PROJECT PERIOD
DIRECT COSTS ONLY

BUDGET CATEGORY TOTALS	INITIAL BUDGET PERIOD *(from Form Page 4)*	2nd ADDITIONAL YEAR OF SUPPORT REQUESTED	3rd ADDITIONAL YEAR OF SUPPORT REQUESTED	4th ADDITIONAL YEAR OF SUPPORT REQUESTED	5th ADDITIONAL YEAR OF SUPPORT REQUESTED
PERSONNEL: *Salary and fringe benefits. Applicant organization only.*	2,277	8,644			
CONSULTANT COSTS					
EQUIPMENT					
SUPPLIES		27,000			
TRAVEL					
INPATIENT CARE COSTS					
OUTPATIENT CARE COSTS					
ALTERATIONS AND RENOVATIONS					
OTHER EXPENSES					
DIRECT CONSORTIUM/ CONTRACTUAL COSTS					
SUBTOTAL DIRECT COSTS *(Sum = Item 8a, Face Page)*	2,277	35,644			
F&A CONSORTIUM/ CONTRACTUAL COSTS					
TOTAL DIRECT COSTS	2,277	35,644			

TOTAL DIRECT COSTS FOR ENTIRE PROPOSED PROJECT PERIOD	**$** 37,921

JUSTIFICATION. Follow the budget justification instructions exactly. Use continuation pages as needed.

Personnel

A. Senior/Key Personnel

Sid E. O'Bryant, Ph.D. (UNTHSC; Co-Principal Investigator) will commit 1% of his annual effort to completion of this study. He is also a global leader in the field of blood-based biomarkers of neurodegenerative disease, having been the first to cross-validate a blood-based AD screener across independent cohorts. He is also the lead of an international working group designed to generate best practices / guidelines for research into blood-based biomarkers of AD (O'Bryant et al 2015). He designed and runs the blood-based biomarkers studies of the Texas Alzheimer's Research & Care Consortium and is the Chair of the Professional Interest Area on Blood Based Biomarkers of the Alzheimer's Association. As the Co-PI, he will be responsible for oversight of all proteomic assays and analytics of this study, including ensuring timely collection of data, oversight of laboratory personnel conducting ECL assays, database entry and QC processes, data analysis and interpretation, as well as preparation of manuscripts and presentations of obtained data. (Continued...)

Fan Zhang, Ph.D. (UNTHSC; Co-Investigator) will devote 2% of his effort in Year 2 towards to this project. Dr. Zhang has extensive experience in bioinformatics and has worked extensively with the O'Bryant laboratory on blood-based analyses, inclusing SVM analyses. He will work with Dr. O'Bryant to generate and refine the bioinformatic models to test the hypotheses proposed in this grant and generate alternative models as necessary. He will also work with the investigators for additional data analytics and the generation of manuscripts from obtained data.

B. Other Research Personnel

Research Assistant (TBD). The Research Assistant will spend 10% of his/her effort in Year 2 towards the completion of this study. S/He will be responsible for processing of blood samples and conducting ECL assays under the supervision of Dr. O'Bryant.

C. Supplies.

A total of $100 per person has been allocated for assay supplies (n=250 samples) for a total of $25,000. year has been allocated towards purchase of proteomic assay supplies. Additionally, $2,000 in lab supplies have been allocated for tips, tubes, cryovials, labels and other supplies that become necessary.

BIOGRAPHICAL SKETCH

NAME	POSITION TITLE
Sid E. O'Bryant, Ph.D.	Associate Professor & Director, Center for Alzheimer's & Neurodegenerative Disease Research (CANDR) University of North Texas Health Science Center
eRA COMMONS USER NAME SOBRYANT79430	

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	YEAR(s)	FIELD OF STUDY
Louisiana State University, Baton Rouge, LA	BS	12/1998	Psychology
University at Albany, SUNY, Albany NY	Ph.D.	7/2004	Clinical Psychology
UMMC/VA Medical Center Consortium, Jackson, MS	Internship	7/2003-6/04	Neuropsychology
New Orleans VA Medical Center, New Orleans LA	Fellowship	7/2004-6/05	Neuropsychology

A. Personal Statement: I have significant experience relevant to the research proposed within this application to make me highly qualified as PI. I am a global leader in the area of blood-based biomarkers of cognitive dysfunction and Alzheimer's disease (AD). I led the team that generated a blood-based algorithm approach in the Texas Alzheimer's Research & Care Consortium (TARCC) cohort that yielded excellent accuracy in detecting AD and our team was then the first to cross-validate such an approach across cohorts analyzing data from the Alzheimer's Disease Neuroimaging Initiative (ADNI). I have cross-validated our work across species (humans and mice), tissues (brain and blood) and biomarker platforms (luminex and ECL). I have also begun applying our methods to the differential diagnosis of multiple neurodegenerative diseases. Our recent data shows the existence of a proinflammatory endophenotype across neurodegenerative diseases (human and animal models) that predict multiple clinical outcomes including treatment response to anti-inflammatory medications. I generated an international collaboration of investigators willing to share existing biorepository samples and associated clinical data and this collaboration supports the current application. I am the Chair of the Blood Based Biomarker Professional Interest Area of the Alzheimer's Association and led the international working group that generated the first ever consensus guidelines for this field of study. I have also conducted proteomic analyses across neurodegenerative disease, including the pilot analyses for this grant proposal. Therefore, I am well-suited the PI on the current proposal.

1. O'Bryant, SE, Xiao, G, Barber, R, Reisch, J, Doody, R, Fairchild, T, Adams, P, Waring, S, & Diaz-Arrastia, R. for the Texas Alzheimer's Research Consortium. (2010). A serum protein-based algorithm for the detection of Alzheimer's disease. *Archives of Neurology, 67*(9), 1077-1081. PMID: 20837851
2. O'Bryant, SE, Xiao, G, Barber, R, Reisch, J, Hall, J, Cullum, CM, Doody, R, Fairchild, T, Adams, P, Wilhelmsen, K & Diaz-Arrastia, R (2011). A blood-based algorithm for the detection of Alzheimer's disease. *Dementia and Geriatric Cognitive Disorders, 32*, 55-62. PMID: 21865746
3. O'Bryant, SE, Xiao, G, Barber, R, Huebinger, R, Wilhelmsen, K, Edwards, M, Graff-Radford, N, Doody, R, Diaz-Arrastia, R (2011). A blood-based screening tool for Alzheimer's disease that spans serum and plasma: Findings from TARC & ADNI. *PLoS ONE*, 6(12): e28092. doi:10.1371/journal.pone.0028092. PMID:22163278
4. O'Bryant SE, Xiao G, Zhang F, Edwards M, German DC, Yin X et al (2014). Validation of a serum screen for Alzheimer's disease across assay platforms, species and tissues. *Journal of Alzheimer's Disease*, 42(2): 1325-35. PMID: 25024345.

B. Positions and Honors

Positions

2005- 2011 Assistant Professor, TX Tech Health Science Center, Department of Neurology, Lubbock, TX
2005- 2011 Adjunct faculty, Department of Psychology, Texas Tech University, Lubbock, TX
2005- 2011 Affiliate Health Staff Member, University Medical Center, Lubbock, TX
2008- 2011 Director of Research, F. Marie Hall Institute for Rural and Community Health, Texas Tech University Health Sciences Center, Lubbock, TX
2012- Associate Professor and Director of Translational Aging and Alzheimer's Disease Research, Department of Internal Medicine, University of North Texas Health Science Center, Ft Worth, TX
2014- Director, Center for Alzheimer's & Neurodegenerative Disease Research University of North Texas Health Science Center, Fort Worth, TX.

Honors

1998 National Academy of Neuropsychology conference poster award
2006-2010 National Institutes of Health (NIH) – Health Disparities Loan Repayment Program Awardee
2006 Selected to attend the 20th Annual National Institute on Aging (NIA) Summer Institute on Aging Research
2009 Nelson Butters Award, National Academy of Neuropsychology
2009 Early Career Award, National Academy of Neuropsychology
2010 Texas Tech University Chancellor's Council Distinguished Research Award
2010 Fellow, National Academy of Neuropsychology
2011 Early Career Conference Travel Award, American Psychological Association
2012 "40 Under 40" awardee for Tarrant, County Texas.
2013 Disparities Committee member of the National Alzheimer's Plan, Alzheimer's Disease Related Dementias workshop
2013 Federation of Associations in Behavioral & Brain Sciences (FABBS) Early Career Investigator Award – Sponsored by the National Academy of Neuropsychology
2014 Early Career Service Award, National Academy of Neuropsychology

Other Experience and Professional Service

2006-2008 Associate Editor, Journal of Psychopathology and Behavioral Assessment
2007-Present Editorial Board, Archives of Clinical Neuropsychology
2008 Member – Scientific Advisory Committee of the American Psychology Association – Div 40
2009-2011 Member – Committee on Rural Health, American Psychological Association
2012-present NIH Study Sections – NST-1, ZAG1 ZIJ-6, ZNS1 SRB-M
2013 Alzheimer's Association grant reviewer
2013-present Associate Editor – Journal of Alzheimer's Disease
2013 Chair, Blood Based Biomarker Professional Interest Area (PIA) of the International Society to Advance Alzheimer's Research and Treatment (ISTAART) of the Alzheimer's Association
2014 Chair, Consortium for the Establishment of Biomarkers Across Neurodegenerative Diseases (CE-BAND)

C. Contributions to Science

1. I am global leader in the area of blood-based biomarkers of AD and cognitive loss. This work began with the search for a simple, reliable and cost-effective tool for detecting AD within primary care settings. Current state-of-the-art diagnosis includes a comprehensive specialty examination that includes a dementia specialist physician, neuroimaging, clinical labs and neuropsychological testing. However, to date, there is no rapid and cost-effective means for the primary care providers to make informed decisions as to which patients require referral for such specialty examinations. We have generated and cross-validate (across cohorts, assay platforms [luminex, ECL], species [humans and animal models] and tissue [brain, serum, plasma]) a blood-based algorithm that is highly accurate in detecting AD (see publications listed above). This work has set the stage for many other laboratories that have modeled our methods for the design of similar approaches for blood-based biomarker profiles of AD as well as other neurodegenerative diseases. This work has also led to the generation of an international working group designed to move the field forward towards clinical practice, which I chair.

a. Laske C, Sohrabi HR, Frost SM, Lopez-De-Ipina K, Gerrard P, Buscema M, Dauwels J, Soekadar SR, Mueller S, Linnemann C, Bridgenbaugh SA, Kanagasingam Y, Martins RN & O'Bryant SE. (2015). Innovative diagnostic tools for early detection of Alzheimer's disease. Alzheimer's & Dementia, 11(5), 561-78.
b. O'Bryant SE, Gupta V, Henriksen K, Edwards M, Jeromin A, Lista S, Bazenet C, Soares H, Lovestone S, Hampel H, Montine T, Blennow K, Foroud T, Carrillo M, Graff-Radford N, Laske C, Breteler M, Shaw L, Trojanowski JQ, Schupf N, Rissman R, Fagan A, Oberoi P, Umek R, Weiner MW, Grammas P, Posner H & Martins R (2015). Guidelines for the standardization of preanalytic variables for blood-based biomarker studies in Alzheimer's disease research. *Alzheimer's & Dementia, 11(5*), 549-60. PMID: 25282381.
c. Snyder HM, Carrillo MC, Grodstein F, Henriksen K, Jeromin A, Lovestone S, Mielke MM, O'Bryant SE et al (2014). Developing novel blood-based biomarkers for Alzheimer's disease. *Alzheimer's & Dementia, 10*(1): 109-14. PMID: 24496073.
d. Kenriksen K, O'Bryant SE, Hampel H, Trojanowski JQ, Montine TJ, Jeromin A, Blennow K, Lonneborg A, Wyss-Coray T, Soares H, Bazenet C, Sjogren M, Hu Wm Lovestone S, Karsdal MA, & Weiner MW (2013). The future of blood-based biomarkers for Alzheimer's disease. *Alzheimer's & Dementia, 10(1)*:115-31. PMID:23850333

2. I have worked extensively in the area of cognitive aging research among underserved populations. I have been responsible for building multiple cohorts targeting both rural (Project FRONTIER) and Mexican American (HABLE study) adults and elders targeting factors related to cognitive aging. Our team has a strong passion and desire to reach underserved groups for inclusion in cutting-edge cognitive aging research, including clinical trials. Over the last several years, I have been responsible for the recruitment of >1,500 Hispanic adults and elders into research.

a. O'Bryant, SE, Johnson LA, Reisch J, Edwards M, Hall J, Barber R, Devous M, Royall D & Sing M (2013). Risk factors for mild cognitive impairment among Mexican Americans. *Alzheimer's & Dementia, 9(6)*: 622-631. PMID:23800829.
b. O'Bryant SE, Xiao G, Edwards M, Devous MD, Gupta VB, Martins R, Zhang F, & Barber RC for the Texas Alzheimer's Research and Care Consortium (2013). Biomarkers of Alzheimer's disease among Mexican Americans. *Journal of Alzheimer's Disease, 34*(4): 841-9. PMID: 23313927
c. O'Bryant SE, Johnson LA, Edwards M, Soares H, Devous MD, Ross S, Rohlfing G & Hall J (2013). The link between C-reactive protein and Alzheimer's disease among Mexican Americans. *Journal of Alzheimer's Disease, 34*(3): 701-6. PMID: 23254637
d. Johnson LA, Gamboa A, Vintimilla R, Cheatwood AJ, Grant A, Trivedi A, Edwards M, Hall JR & O'Bryant SE (2015, in press). Comorbid depression and diabetes as a risk for mild cognitive impairment and Alzheimer's disease in elder Mexican Americans. *Journal of Alzheimer's Disease*.

3. I have spent a great deal of time and effort working towards understanding the diagnostic accuracy of clinical instruments (as well as clinical biomarkers). Many clinical instruments are utilized regularly without a full appreciation of the underlying psychometric properties as they relate to the particular setting. In this work, we provided a framework for the interpretation of several commonly utilized clinical instruments (in practice, research and clinical trials), which has supported a wide variety of research laboratories. I am now applying these same methods towards the development of guidelines for moving blood-based biomarkers of neurodegeneration towards clinical utility.

a. Spering C, Hobson, V, Lucas, JA, Menon CV, Hall, JR, & O'Bryant SE (2012). Diagnostic accuracy of the MMSE in detecting Probable Alzheimer's disease in ethnically diverse highly educated individuals: An analysis of the NACC database. *Journal of Gerontology: Medical Sciences, 67(8): 890-6.* PMID: 22396476
b. O'Bryant, S.E., Humphreys, J.D., Smith, G.E., Ivnik, R.J., Graff-Radford, N.R., Petersen, R.C., & Lucas, J.A. (2008). Detecting dementia with the Mini-Mental State Examination (MMSE) in highly educated individuals. *Archives of Neurology, 65*(7), 963-967.

c. O'Bryant, S.E. & Lucas, J.A. (2006). Estimating the predictive value of the Test of Memory Malingering: An illustrative example for clinicians. *The Clinical Neuropsychologist, 20(3)*, 533-540.
d. Duff, K, Humphreys, JD, O'Bryant, SE, Mold, JW, Schiffer, RB, & Sutker, PB (2008). Utility of the RBANS in detecting cognitive impairment associated with Alzheimer's disease: Sensitivity, specificity, and positive and negative predictive powers. *Archives of Clinical Neuropsychology*, 23(5), 603-12.

4. Over the years, the skill I have honed the most and work that has generated the most productivity has been through my work developing and leading team translational science. I have been responsible for building and managing multiple cohorts (urban and rural, clinic and community-based, minority and non-minority). In addition to the cohorts, I have been responsible for building fully translational teams and research programs that leverage these cohorts. Through this work, I have fostered the academic careers of many investigators, both junior and senior. The translational infrastructures have covered proteomics, animal models, clinical cohorts, community-based cohorts and clinical trials. I have provided the opportunity for many basic scientists to test their findings/theories in humans, but have also worked with clinical and epidemiological scientists to translate findings back into animal models.

a. Hall JR, Wiechmann AR, Cunningham RL, Johnson LA, Edwards M, Barber RC, Singh M, Winter S & O'Bryant SE (in press, 2015). Total testosterone and neuropsychiatric symptoms in elderly men with Alzheimer's. *Alzheimer's Research & Therapy*.
b. Edwards M, Balldin VH, Hall J & O'Bryant SE (2014). Combining select neuropsychological assessments with blood-based biomarkers to detect mild Alzheimer's disease: A molecular neuropsychology approach. *Journal of Alzheimer's Disease, 42*(2): 635-40.
c. Roane BM, Johnson LA, Edwards M, Hall J, Al-Farra S, O'Bryant SE (2014). The link between sleep disturbance and depression among Mexican Americans: A Project FRONTIER study. *Journal of Clinical Sleep Medicine, 10*(4): 427-31.
d. Cunningham RL, Singh M, O'Bryant SE, Hall JR, & Barber RC (2014). Oxidative stress, testosterone, and cognition among Caucasian and Mexican American men with and without Alzheimer's disease. *Journal of Alzheimer's Disease, 40*(3): 563-73.

A current list of published work in MyBibliography:
http://www.ncbi.nlm.nih.gov/sites/myncbi/sid.o'bryant.1/bibliography/42727847/public/?sort=date&direction=ascending

D. Research Support
Ongoing

T-817 Toyama Chemical in Alzheimer's Disease (TCAD) (O'Bryant, Site PI) 1/2/2015 – 4/1/2017
Toyama Chemical Co., Ltd. – an Alzheimer's Disease Cooperative Studies (ADCS) study
A Phase 2 multi-center, randomized, double blind, placebo-controlled, parallel group study to evaluate the efficacy and safety of T817Mas in patients with mild to moderate Alzheimer's disease (US202).

Pfeiffer Foundation Johnson (PI) 9/1/14 – 8/31/16
Using Cymbalta to treat depression-related memory loss among specific subsets of patients diagnosed with Mild Cognitive Impairment (MCI).
Role: Co-I
Project Summary: This project is designed to understand how specific symptoms of depression are related to the development and progression of mild cognitive impairment (MCI) and to conduct a proof-of-concept clinical trial to treat depression-related memory loss.

138980111.1.2 O'Bryant (PI) 6/1/2013-9/31/2016
Community-Based Primary Care for the Elderly

Centers for Medicare & Medicaid Services (CMS): Delivery System Reform Incentive Payments (DSRIP) program
Project Summary: The goal of this program is the provision of primary care services to underserved elders within community-based settings. It is anticipated that over 3,000 elderly patients will receive care directly from this medical program with a total of a minimum of 15,000 patient visits.

138980111.2.5 Knebl (PI) 6/1/2013-9/31/2016
Discharge Planning for Medicaid Eligible Elders
Centers for Medicare & Medicaid Services (CMS): Delivery System Reform Incentive Payments (DSRIP) program
Role: Co-Investigator
Project Summary: The goal of this program is the provision of comprehensive discharge planning and follow-up to 750 hospitalized Medicaid eligible elders with the primary objective of reducing hospital readmissions.

RS0017 O'Bryant (Site Co-I) 10/31/2006-8/31/2017
Genetic and Biomarkers Study of Alzheimer's
Disease: A Collaborative Effort of the Texas Alzheimer's Disease Research & Care Consortium (TARCC)
Texas Counsel on Alzheimer's Disease and Related Disorders
The goal of this Consortium is to identify novel genetics and biomarkers associated with Alzheimer's disease presence as well as progression. A major theme is the establishment of a blood-test for screening purposes that can be implemented broad-based, which the current PI has lead since study inception.
Role: UNTHSC site Co-I (2012 – present), TTUHSC site PI 2006 – 2011

P30AG12300 Rosenberg (PI) 3/1/2013 – 6/1/2016
Neurobiology of Alzheimer's Disease and Aging
NIH/National Institute on Aging (NIA)
Principal Investigator: Roger Rosenberg, MD
Role – Co-Investigator
Project Summary: My role is as Co-Chair of Biomarkers Subcommittee. My lab is running serum-based biomarkers on AD and non-AD dementia cases from the ADC biobank. We are investigating novel blood-based biomarkers of neuroimaging correlates of AD and cognitive failure as well as non-AD neurodegenerative diseases.

Recently Completed

1R01AG039389-01A1 O'Bryant (PI) 4/15/2012-3/31-2015
A Blood Based Screener for Alzheimer's Disease
National Institute on Aging (NIA)
The goals of this project were to validate our previously generated blood screener for AD on an independent assay platform, compare the screener to neuropathologically confirmed AD cases, and establish the reliability of the screener over time.

RD834794-01 O'Bryant (PI) 3/1/2010-2/28/2014
Development and Validation of the Cumulative Environmental Exposure Index for Arsenic: A Novel Environmental Public Health Indicator –
Environmental Protection Agency (EPA)

BIOGRAPHICAL SKETCH

NAME: Zhang, Fan, Ph.D.

eRA COMMONS USER NAME (credential, e.g., agency login): fanzhan

POSITION TITLE: Research Assistant Professor of Molecular and Medical Genetics, University of North Texas Health Science Center, Graduate School of Biomedical Sciences

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
Harbin Institute of Technology	B.S.	07/1996	Hydraulic Transmission and Control
Harbin Institute of Technology	M.S.	07/1998	Flight Mechanics
Harbin Institute of Technology	Ph.D.	08/2001	General Mechanics
Tsinghua University	Postdoctoral	09/2003	Computer Science
University of California, San Diego	Postdoctoral	07/2008	Bioinformatics
Indiana University-Purdue University Indianapolis	Postdoctoral	10/2011	Bioinformatics

A. Personal Statement

I have over 10 years of experience as a principal and co-investigator in the areas of bioinformatics, data modeling, machine learning and data visualization. I have published about 18 scientific papers in the fields. I also built four databases for data presentation: PEPPI, HOMER, IPAD, and SASD, and published two book chapters for data analysis and presentation: 1)“Data Mining Methods in Omics-Based Biomarker Discovery” for the book “Bioinformatics for Omics Data: Methods and Protocols (Methods in Molecular Biology)” and 2) “Computational Discovery, Verification, and Validation of Functional Biomarkers,” (Royal Society of Chemistry of the United Kingdom). From 2005- 2008, I was a PI responsible for 2 collaborative research projects: 1) Functional site analysis in proteins of G Protein Signaling Pathways using fuzzy evolutionary trace method and its integrated and component-based software design; and 2) Study on Linkage Analysis in Gene Mapping for Teen's depression. The two works focused on biostatistics and data visualization such as three dimension mapping and visualization for binding sites and allele mapping visualization. I also was a co-investigator for providing data analysis and data visualization for several other projects. These projects illustrate my relevant experience in data modeling, machine learning, and data visualization. My major role in this proposal is to develop an integrative data mining method for building prediction model with blood biomarkers for neurodegenerative diseases.

B. Positions and Honors (Past 30 years)

Positions and Employment

2005 -2006 associate professor, Biomedical Engineering School, Capital University of Medical Sciences, and director of biomedical informatics lab, Beijing, China

2006 -2008 postdoc, Department of Radiology, University of California San Diego Medical School, San Diego, CA

2008 -2011 postdoc, School of Informatics, Indiana University-Purdue University Indianapolis, Indianapolis, IN

2011 -2012 data analyst, Department of Nephrology, Mount Sinai School of Medicine, NY

2012 - 2015 bioinformatician, Department of Academic and Institutional Resources and Technology, University of North Texas Health Science Center, Fort Worth, TX

2015 - Present Research Assistant Professor, Department of Molecular and Medical Genetics, University of North Texas Health Science Center, Fort Worth, TX

Other Experiences and Professional Memberships (Selected)

2012 - Member, Institute of Applied Genetics, UNTHSC

Honors

C. Contributions to Science

1. Novel Alternative Splicing Isoform Biomarkers Identification from High-Throughput Plasma Proteomics Profiling of Breast Cancer: Alternative splicing isoform represents a new class of diagnostic biomarkers. Recent scientific evidence is demonstrating that the differentiation and quantification of individual alternative splicing isoforms could improve insights into disease diagnosis and management. Identifying and characterizing alternative splicing isoforms are essential to the study of molecular mechanisms and early detection of complex diseases such as breast cancer. The approach includes three steps: 1) building a synthetic database of alternative splicing isoforms for proteomics experiments; 2) identification, characterization of alternative splicing isoform using proteomics; and 3) validation of alternative splicing isoform. The approach can help generate novel hypotheses on molecular risk factors and molecular mechanisms of cancer in early stage, leading to identification of potentially highly specific alternative splicing isoform biomarkers for early detection of cancer.

a. **Fan Zhang**, Mu Wang, Tran Michael, Renee Drabier. (2013) Novel Alternative Splicing Isoform Biomarkers Identification from High-Throughput Plasma Proteomics Profiling of Breast Cancer. *BMC Systems Biology* [PMID: 24565027]
b. **Fan Zhang** and Renee Drabier. (2013). SASD: the Synthetic Alternative Splicing Database for Identifying Novel Isoform from Proteomics. *BMC Bioinformatics* [PMID: 24267658]
c. **Fan Zhang** and Renee Drabier. (2012) IPAD: the Integrated Pathway Analysis Database for Systematic Enrichment Analysis. *BMC Bioinformatics* Vol. 13 Suppl 14 [PMID: 23046449]
d. Ao Zhou*, **Fan Zhang***, and Jake Y. Chen (2010) PEPPI: A Peptidomic Database of Human Protein Isoforms for Proteomics Experiments, *BMC Bioinformatics*, Vol. 11, Supplement 6, S7 (* co-first author) [PMID:20946618].

2. Biomarker Identification and Data mining: I finished a variety of projects targeting a better understanding of disease mechanisms, diagnosis and therapy of various diseases, especially cancers. The works helped the laboratory findings be transferred quickly to the clinic, enabled the understanding of the translational science underlying diseases and cancers, applied the understanding of disease to improve prevention, diagnosis, and treatment, and fostered research that is interdisciplinary and translational in nature.

a. S. E. O'Bryant, G. Xiao, **F. Zhang**, M. Edwards, D. C. German, X. Yin*, et al.*, "Validation of a serum screen for Alzheimer's disease across assay platforms, species, and tissues," *J Alzheimers Dis,* vol. 42, pp. 1325-35, 2014.
b. D. German, P. O'Suilleabhain, **F. Zhang**, and S. O'Bryant, "ALZHEIMER'S DISEASE AND PARKINSON'S DISEASE: BLOOD BIOMARKER DIFFERENCES," *Alzheimer's & Dementia,* vol. 10, p. P348, 7// 2014.
c. O'Bryant SE, Xiao G, Edwards M, Devous M, Gupta VB, Martins R, **Zhang F**, Barber R, Texas Alzheimer's R, Care C: (2013) Biomarkers of Alzheimer's disease among Mexican Americans. Journal of Alzheimer's disease : JAD 2013, 34(4):841-849 [PMID: 23313927]
d. Huebinger RM, Xiao G, Wilhelmsen KC, Diaz-Arrastia R, **Zhang F**, O'Bryant SE, Barber RC (2012): Comparison of protein concentrations in serum versus plasma from Alzheimer's patients. Advances in Alzheimer's Disease 2012, 1(3):51-58 [link].

3. Pathway Analysis: My another work about pathway analysis and systems biology is essential to the understanding molecular mechanisms of panel protein biomarkers and can lead to improved diagnostics, therapies, and perhaps preventive measures for disease.

a. **Fan Zhang** and Renee Drabier. (2014). Pathway-based biomarkers for breast cancer in proteomics. *Cancer Bioinformatics* [accepted]
b. **Fan Zhang**, Youping Deng and Renee Drabier. (2013) Multiple Biomarker Panels for Early Detection of Breast Cancer in Peripheral Blood. *BioMed Research International* [PMID: 24371830]
c. **Fan Zhang**, Jake Chen, Mu Wang, Renee Drabier: (2013) A Neural Network Approach to Multi-biomarker Panel Discovery by High-Throughput Plasma Proteomics Profiling of Breast Cancer. GLBIO 2013, PITTSBURGH, May 14-16, 2013 BMC Proceedings, [PMID: 24565503]
d. **Fan Zhang** and Renee Drabier. (2012) IPAD: the Integrated Pathway Analysis Database for Systematic Enrichment Analysis. *BMC Bioinformatics* Vol. 13 Suppl 14 [PMID: 23046449]

Complete List of Published Work

D. Research Support

Ongoing Research Support

RF9990 Sid (PI) 9/01/13 – 8/31/16

Community-Based Primary Care for the Elderly, funded by the Centers for Medicare and Medicaid Services.
The major goal of this project is to provide medical care to near elders (age 50+) and Medicaid eligible elders (age 65+) within community-based settings (e.g. senior citizen centers, food banks, churches) and clinics..
Role: Co-Investigator

Completed Research Support (Prior Three Years)

5R01AG039389-02 Sid (PI) 4/2012- 3/2015

A blood-based screening tool for Alzheimer's disease, funded by National Institute on Aging
The goal of this project is to identify biomarkers for Alzheimer's disease.
Role: Co-Investigator

RESOURCES

Follow the 398 application instructions in Part I, 4.7 Resources.

Facilities & Other Resources - There is a very well established infrastructure and supportive environment to ensure the success of this project.

University of North Texas Health Science Center (UNTHSC). In my role as the Director of the Center for Alzheimer's & Neurodegenerative Disease Research (CANDR; https://www.unthsc.edu/health-institutes/institute-for-healthy-aging/) and Director of the Translational Research Program at UNTHSC, I have the basic laboratory and clinical laboratory space for the completion of this study.

Basic Laboratory: My basic laboratory space consists of approximately 600 square feet. I have all of the basic laboratory equipment (see Equipment section) to complete this study. My proteomics laboratory serves as a core biomarker facility for multiple local, US and international scientists, including clinical trials and the recently funded Biomarkers of Alzheimer's Disease among Down Syndrome initiative. CANDR consists of multiple funded investigators spanning public health, neuroscience, psychology, genetics and biostatistics. CANDR is part of the UNTHSC Institute for Healthy Aging (IHA), which includes multiple P-grant and R01-grant funded investigators. Therefore, the overall facilities are more than capable for conducting the proposed wet-lab proteomics work.

Clinical Research Laboratory: The Translational Research Program has over 1500 sq ft of clinical research office space and 12 full- and part-time employees. Our group consists of 4 certified promotora as well as a certified translator. This research team has recruited over 2,000 (approx. 50% Hispanic) adults and elders into research studies over the last 3 years.

Health & Aging Brain among Latino Elders (HABLE) study. The HABLE study is a longitudinal, community-based research study of cognitive aging among Mexican American adults and elders in the Dallas – Fort Worth (DFW) community. Over 600 Mexican Americans have been part of the program to date and the group always has a wait list of >100 participants wanting to become part of the study. We have also recruited non-Hispanic whites into this study for feasibility purposes and comparison studies. We have a 98% agreement of HABLE participants to provide blood samples for the biorepository and >99% agreement into neuroimaging substudies (MRI and PET) conducted to date. The HABLE study follows a Community-Based Participatory Research (CBPR) approach. As such, the HABLE Community Advisory Board provides input into all research projects. Additionally, the HABLE study provides results back to participants from the clinical laboratory exams, neuropsychological testing and imaging studies (i.e. anything in regular clinical use). All research participants decide if and how they would like feedback (self only, primary care provider only, both, none). To date, the HABLE study has provided approximately $500,000.00 back to the community when participant payments ($20/hr per our IRB approved protocol) and clinical blood work. HABLE has current IRB approval. Our extensive community-based network through these efforts will make recruitment into the proposed study readily achievable.

Intellectual Rapport. The UNTHSC IHA is home to one of the most funded basic science groups by the NIH in the state of Texas. Drs. Meharvan (Sonny) Singh and Michael Forester are amongst these eminent scholars that the PI collaborates with through the IAADR. The overall facilities and resources for this grant are well-equipped and experienced experiences to complete the current project. The infrastructure will also benefit greatly from this grant as it builds additional collaborative relationships within the research groups that will lead to future large-scale collaborative studies of biomarkers of aging.

Program Director/Principal Investigator (Last, First, Middle): O'Bryant, Sid E.

CHECKLIST

TYPE OF APPLICATION *(Check all that apply.)*

☒ NEW application. *(This application is being submitted to the PHS for the first time.)*

☐ RESUBMISSION of application number: _____
(This application replaces a prior unfunded version of a new, renewal, or revision application.)

☐ RENEWAL of grant number: _____
(This application is to extend a funded grant beyond its current project period.)

☐ REVISION to grant number: _____
(This application is for additional funds to supplement a currently funded grant.)

☐ CHANGE of program director/principal investigator.

Name of former program director/principal investigator: _____

☐ CHANGE of Grantee Institution. Name of former institution: _____

☐ FOREIGN application ☐ Domestic Grant with foreign involvement List Country(ies) Involved:

INVENTIONS AND PATENTS *(Renewal appl. only)* ☒ No ☐ Yes

If "Yes," ☐ Previously reported ☐ Not previously reported

1. PROGRAM INCOME ***(See instructions.)***
All applications must indicate whether program income is anticipated during the period(s) for which grant support is request. If program income is anticipated, use the format below to reflect the amount and source(s).

Budget Period	Anticipated Amount	Source(s)
None	$0.00	

2. ASSURANCES/CERTIFICATIONS ***(See instructions.)***
In signing the application Face Page, the authorized organizational representative agrees to comply with the policies, assurances and/or certifications listed in the application instructions when applicable. Descriptions of individual assurances/certifications are provided in Part III and listed in Part I, 4.1 under Item 14. If unable to certify compliance, where applicable, provide an explanation and place it after this page.

3. FACILITIES AND ADMINSTRATIVE COSTS (F&A)/ INDIRECT COSTS. See specific instructions.

☒ DHHS Agreement dated: 6/4/2013 ☐ No Facilities And Administrative Costs Requested.

☐ DHHS Agreement being negotiated with _____ Regional Office.

☐ No DHHS Agreement, but rate established with _____ Date _____

CALCULATION* *(The entire grant application, including the Checklist, will be reproduced and provided to peer reviewers as confidential information.)*

a. Initial budget period:	Amount of base $	2,277	x Rate applied	46.00%	% = F&A costs	$	1,047
b. 02 year	Amount of base $	35,644	x Rate applied	46.00%	% = F&A costs	$	16,396
c. 03 year	Amount of base $		x Rate applied	0.00%	% = F&A costs	$	
d. 04 year	Amount of base $		x Rate applied	0.00%	% = F&A costs	$	
e. 05 year	Amount of base $		x Rate applied	0.00%	% = F&A costs	$	
					TOTAL F&A Costs	$	17,444

*Check appropriate box(es):

☐ Salary and wages base ☒ Modified total direct cost base ☐ Other base *(Explain)*

☐ Off-site, other special rate, or more than one rate involved *(Explain)*

Explanation *(Attach separate sheet, if necessary.):*

4. DISCLOSURE PERMISSION STATEMENT: If this application does not result in an award, is the Government permitted to disclose the title of your proposed project, and the name, address, telephone number and e-mail address of the official signing for the applicant organization, to organizations that may be interested in contacting you for further information (e.g., possible collaborations, investment)? ☒ Yes ☐ No

Department of Health and Human Services
Public Health Services

Grant Application

Do not exceed character length restrictions indicated.

LEAVE BLANK—FOR PHS USE ONLY.

Type	Activity	Number
Review Group		Formerly
Council/Board (Month, Year)		Date Received

1. TITLE OF PROJECT *(Do not exceed 81 characters, including spaces and punctuation.)*

Plasma Biomarkers in Lewy Body Disease

2. RESPONSE TO SPECIFIC REQUEST FOR APPLICATIONS OR PROGRAM ANNOUNCEMENT OR SOLICITATION ☐ NO ☒ YES
(If "Yes," state number and title)

Number: NACC2016-COLLAB Title: NACC-funded Collaborative Projects, FY2016

3. PROGRAM DIRECTOR/PRINCIPAL INVESTIGATOR

3a. NAME (Last, first, middle)	3b. DEGREE(S)	3h. eRA Commons User Name
Rosenberg, Roger	MD	

3c. POSITION TITLE
Chair

3e. DEPARTMENT, SERVICE, LABORATORY, OR EQUIVALENT
Neurology & Neurotherapeutics, Physiology

3f. MAJOR SUBDIVISION
Neurology Clinic

3g. TELEPHONE AND FAX *(Area code, number and extension)*
TEL: 972-645-8800 FAX: 214-645-8300

3d. MAILING ADDRESS *(Street, city, state, zip code)*
Neurology Clinic
James W. Aston Ambulatory Care Center
5303 Harry Hines Blvd, 4th Floor
Dallas, TX 75390-8869

E-MAIL ADDRESS:
Roger.Rosenburg@UTSouthwestern.edu

4. HUMAN SUBJECTS RESEARCH	4a. Research Exempt	If "Yes," Exemption No.
☐ No ☒ Yes	☒ No ☐ Yes	

4b. Federal-Wide Assurance No.	4c. Clinical Trial	4d. NIH-defined Phase III Clinical Trial
A00005412	☐ No ☒ Yes	☒ No ☐ Yes

5. VERTEBRATE ANIMALS ☒ No ☐ Yes — 5a. Animal Welfare Assurance No A3329-01

6. DATES OF PROPOSED PERIOD OF SUPPORT *(month, day, year—MM/DD/YY)*		7. COSTS REQUESTED FOR INITIAL BUDGET PERIOD		8. COSTS REQUESTED FOR PROPOSED PERIOD OF SUPPORT	
From	Through	7a. Direct Costs ($)	7b. Total Costs ($)	8a. Direct Costs ($)	8b. Total Costs ($)
07/01/16	06/30/18	$15,182	$23,229	$30,719	$47,000

9. APPLICANT ORGANIZATION
Name The University of Texas at Dallas
Address
800 West Campbell Road
Richardson, TX 75080-3021

10. TYPE OF ORGANIZATION
Public: → ☐ Federal ☒ State ☐ Local
Private: → ☐ Private Nonprofit
For-profit: → ☐ General ☐ Small Business
☐ Woman-owned ☐ Socially and Economically Disadvantaged

11. ENTITY IDENTIFICATION NUMBER
75-1305566
DUNS NO.800188161 Cong. District TX-032

12. ADMINISTRATIVE OFFICIAL TO BE NOTIFIED IF AWARD IS MADE
Name Dina Caplinger
Title Grants and Contracts Specialist
Address 800 West Campbell Road, AD15
Richardson, TX 75080-3021
Tel: 972-883-2312 FAX: 972-883-2310
E-Mail: osp@utdallas.edu

13. OFFICIAL SIGNING FOR APPLICANT ORGANIZATION
Name Emily Lacy
Title Assistant Director, Office of Sponsored Projects
Address 800 West Campbell Road, AD15
Richardson, TX 75080-3021
Tel: 972-883-2313 FAX: 972-883-2310
E-Mail: osp@utdallas.edu

14. APPLICANT ORGANIZATION CERTIFICATION AND ACCEPTANCE: I certify that the statements herein are true, complete and accurate to the best of my knowledge, and accept the obligation to comply with Public Health Services terms and conditions if a grant is awarded as a result of this application. I am aware that any false, fictitious, or fraudulent statements or claims may subject me to criminal, civil, or administrative penalties.

SIGNATURE OF OFFICIAL NAMED IN 13. *(In ink. "Per" signature not acceptable.)* DATE

Use only if preparing an application with Multiple PDs/PIs. See http://grants.nih.gov/grants/multi_pi/index.htm for details.

Contact Program Director/Principal Investigator (Last, First, Middle): Rosenberg, Roger

3. PROGRAM DIRECTOR / PRINCIPAL INVESTIGATOR

3a. NAME (Last, first, middle)	3b. DEGREE(S)	3h. NIH Commons User Name
Hart, John	M.D.	JohnHart

3c. POSITION TITLE Professor, Medical Science Director	3d. MAILING ADDRESS *(Street, city, state, zip code)* Center for BrainHealth 2200 West Mockingbird Lane Dallas, TX 75235-5451
3e. DEPARTMENT, SERVICE, LABORATORY, OR EQUIVALENT School of Behavioral and Brain Sciences	
3f. MAJOR SUBDIVISION Center for BrainHealth	
3g. TELEPHONE AND FAX *(Area code, number and extension)* TEL: 972-883-3007 FAX: 972-883-3026	E-MAIL ADDRESS: jhart@utdallas.edu

3. PROGRAM DIRECTOR / PRINCIPAL INVESTIGATOR

3a. NAME (Last, first, middle)	3b. DEGREE(S)	3h. NIH Commons User Name

3c. POSITION TITLE	3d. MAILING ADDRESS *(Street, city, state, zip code)*
3e. DEPARTMENT, SERVICE, LABORATORY, OR EQUIVALENT	
3f. MAJOR SUBDIVISION	
3g. TELEPHONE AND FAX *(Area code, number and extension)* TEL: FAX:	E-MAIL ADDRESS:

3. PROGRAM DIRECTOR / PRINCIPAL INVESTIGATOR

3a. NAME (Last, first, middle)	3b. DEGREE(S)	3h. NIH Commons User Name

3c. POSITION TITLE	3d. MAILING ADDRESS *(Street, city, state, zip code)*
3e. DEPARTMENT, SERVICE, LABORATORY, OR EQUIVALENT	
3f. MAJOR SUBDIVISION	
3g. TELEPHONE AND FAX *(Area code, number and extension)* TEL: FAX:	E-MAIL ADDRESS:

3. PROGRAM DIRECTOR / PRINCIPAL INVESTIGATOR

3a. NAME (Last, first, middle)	3b. DEGREE(S)	3h. NIH Commons User Name

3c. POSITION TITLE	3d. MAILING ADDRESS *(Street, city, state, zip code)*
3e. DEPARTMENT, SERVICE, LABORATORY, OR EQUIVALENT	
3f. MAJOR SUBDIVISION	
3g. TELEPHONE AND FAX *(Area code, number and extension)* TEL: FAX:	E-MAIL ADDRESS:

PROJECT SUMMARY (See instructions):

The purpose of this project is to collect the requisite data and build the necessary collaborative relationships to submit a grant for a large-scale prospective study of the utility of blood-based biomarkers in Lewy Body disease (LBD). The long-term goal of this line of research is the generation of blood-based profiles that have diagnostic, prognostic and theragnostic value in LBD. Given the rapidly growing elderly population, neurodegenerative dementias are a major public health problem. LBD is the 2nd most prevalent neurodegenerative dementia accounting for 15-20% of cases and is often misdiagnosed as Alzheimer's disease (AD). LBD is an α-synuclein disorder that is characterized by Lewy Body and Lewy neurites in specific areas of the brain as well as acetylcholine neuronal degeneration. There is frequent AD and LBD overlap making the differential diagnosis between LBD and AD a significant problem in clinical practice. Additionally, there is an urgent need for methods to predict clinical course in LBD to design trials and monitor interventions. Based on preliminary findings it is our hypothesis that a blood-based biomarker profile can be accurate in detecting and distinguishing LBD from AD and controls. The Specific Aims of this project are as follows: Specific Aim 1 – Replicate our blood-based profile of LBD in a larger sample and Specific Aim 2 – To identify biologically-based subgroups in LBD.

RELEVANCE (See instructions):

Lewy body disease is hard to distinguish from Alzheimer disease because the pathologies overlap. Based on promising preliminary data this study evaluates if a blood based biomarker is able to able to have diagnostic, therapeutic and pathogenic use.

PROJECT/PERFORMANCE SITE(S) (if additional space is needed, use Project/Performance Site Format Page)

Project/Performance Site Primary Location		
Organizational Name: The Center for BrainHealth at The University of Texas at Dallas		
DUNS: 800188161		
Street 1: 2200 West Mockingbird Lane	Street 2:	
City: Dallas	County: Dallas	State: TX
Province:	Country: USA	Zip/Postal Code: 75235-5451
Project/Performance Site Congressional Districts: TX-030		

Additional Project/Performance Site Location		
Organizational Name: The University of Texas Southwestern Medical Center Alzeimers's Disease Center		
DUNS: 800771545		
Street 1: 5323 Harry Hines Blvd	Street 2:	
City: Dallas	County: Dallas	State: TX
Province:	Country: USA	Zip/Postal Code: 75390-8542
Project/Performance Site Congressional Districts: TX-030		

SCIENTIFIC/KEY PERSONNEL. See instructions. *Use continuation pages as needed* to provide the required information in the format shown below. Start with Program Director(s)/Principal Investigator(s). List all other key personnel in alphabetical order, last name first.

Name	eRA Commons User Name	Organization	Role on Project
John Hart, MD	JohnHart	UT Dallas	Co-Investigator

OTHER SIGNIFICANT CONTRIBUTORS

Name	Organization	Role on Project

Human Embryonic Stem Cells ☒ **No** ☐ **Yes**

If the proposed project involves human embryonic stem cells, list below the registration number of the specific cell line(s) from the following list: http://stemcells.nih.gov/research/registry/eligibilityCriteria.asp. *Use continuation pages as needed.*

If a specific line cannot be referenced at this time, include a statement that one from the Registry will be used.

Cell Line

Program Director/Principal Investigator (Last, First, Middle): Rosenberg, Roger

DETAILED BUDGET FOR INITIAL BUDGET PERIOD
DIRECT COSTS ONLY

FROM 07/01/2016 THROUGH 06/30/2017

List PERSONNEL *(Applicant organization only)*
Use Cal, Acad, or Summer to Enter Months Devoted to Project
Enter Dollar Amounts Requested *(omit cents)* for Salary Requested and Fringe Benefits

NAME	ROLE ON PROJECT	Cal. Mnths	Acad. Mnths	Summer Mnths	INST.BASE SALARY	SALARY REQUESTED	FRINGE BENEFITS	TOTAL
John Hart, MD	PD/PI	0.12			185,100	1,851	555	2,406
Penelope Jones	Technician	3			39,224	9,806	2,970	12,776
SUBTOTALS →						11,657	3,525	15,182

CONSULTANT COSTS	
EQUIPMENT *(Itemize)*	
SUPPLIES *(Itemize by category)*	
TRAVEL	
INPATIENT CARE COSTS	
OUTPATIENT CARE COSTS	
ALTERATIONS AND RENOVATIONS *(Itemize by category)*	
OTHER EXPENSES *(Itemize by category)*	

CONSORTIUM/CONTRACTUAL COSTS	DIRECT COSTS	
SUBTOTAL DIRECT COSTS FOR INITIAL BUDGET PERIOD *(Item 7a, Face Page)*		$ 15,182
CONSORTIUM/CONTRACTUAL COSTS	FACILITIES AND ADMINISTRATIVE COSTS	8,047
TOTAL DIRECT COSTS FOR INITIAL BUDGET PERIOD		$ 23,229

BUDGET FOR ENTIRE PROPOSED PROJECT PERIOD
DIRECT COSTS ONLY

BUDGET CATEGORY TOTALS	INITIAL BUDGET PERIOD *(from Form Page 4)*	2nd ADDITIONAL YEAR OF SUPPORT REQUESTED	3rd ADDITIONAL YEAR OF SUPPORT REQUESTED	4th ADDITIONAL YEAR OF SUPPORT REQUESTED	5th ADDITIONAL YEAR OF SUPPORT REQUESTED
PERSONNEL: *Salary and fringe benefits. Applicant organization only.*	15,182	15,537			
CONSULTANT COSTS					
EQUIPMENT					
SUPPLIES					
TRAVEL					
INPATIENT CARE COSTS					
OUTPATIENT CARE COSTS					
ALTERATIONS AND RENOVATIONS					
OTHER EXPENSES					
DIRECT CONSORTIUM/ CONTRACTUAL COSTS					
SUBTOTAL DIRECT COSTS *(Sum = Item 8a, Face Page)*	15,182	15,537			
F&A CONSORTIUM/ CONTRACTUAL COSTS	8,047	8,234			
TOTAL DIRECT COSTS	23,229	23,771			

TOTAL DIRECT COSTS FOR ENTIRE PROPOSED PROJECT PERIOD	**$** 47,000

JUSTIFICATION. Follow the budget justification instructions exactly. Use continuation pages as needed.

John Hart, Jr., M.D., Principal Investigator: Dr. Hart is Co-Director of the Clinical Core of the Alzheimer's Disease Center at the University of Texas Southwestern Medical Center (UTSW). The Johns Hopkins-trained neurologist is also a Professor of Behavioral and Brain Sciences at The University of Texas at Dallas (UT Dallas) with a joint appointment in the departments of Neurology and Psychiatry at UTSW. At UT Dallas, Dr. Hart is Medical Science Director at the Center for BrainHealth, where he also holds the Jane and Bud Smith Distinguished Chair and the Distinguished Chair in Neuroscience. For this project, Dr. Hart will identify and recruit 75 patients per year (150 total) from the UTSW Alzheimer's Disease Center who meet the criteria for Lewy Body Disease to participate in the research study and will oversee all aspects of the proposed research project. This subcontract is being done through UT Dallas because Dr. Hart's primary appointment is through UT Dallas and his salary compensation must be paid through UT Dallas due to UT System rules and regulations.

Penelope Jones, Research Technician: Ms. Jones will conduct the scheduling and blood draw of all research participants under the supervision of Dr. Hart. In addition, she will coordinate the storage, tracking, and shipment of all samples to the analysis site in accordance with the proposed research protocol.

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FIVE PAGES.**

NAME: John Hart, Jr., M.D.

eRA COMMONS USER NAME (credential, e.g., agency login): JohnHart

POSITION TITLE: Professor of Neurology and Psychiatry (UTSW), Professor of Behavioral & Brain Sciences (UTD)

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE	Completion Date	FIELD OF STUDY
The Johns Hopkins University	B.A.	1979	Psychology
University of Maryland School of Medicine	M.D.	1983	Medicine
Union Memorial Hospital, Baltimore, MD	Internship	1983-1984	Medicine
The Johns Hopkins Hospital	Residency	1984-1986	Neurology
The Johns Hopkins Hospital	Fellowship	1995-1996	Cognitive Neurology / Neuropsychology
The Johns Hopkins Hospital	Residency	1986-1990	Neurology

A. Personal Statement

I have worked for over 25 years as a cognitive/behavioral neurologist and neuroscientist focusing on investigations in semantic memory and designing and conducting clinical neuroscience investigations. This includes the protocol design of the neuropsychological and neuroimaging aspects and then conducting the studies as PI in large-scale investigations of Herpes Simplex encephalitis (NIAID), West Nile encephalomyelitis (NIAID), Gulf War Syndrome (VA), PTSD (DOD), and Multiple Sclerosis (NMSS).

1. **Hart, J., Jr,**, Maguire, M.J., Motes, M., Mudar, R.A., Chiang, H.S., Womack, K.B., Kraut, M.A. (2013). Semantic memory retrieval circuit: role of pre-SMA, caudate, and thalamus. *Brain & Language, 126*(1), 89-98. doi: 10.1016/j.bandl.2012.08.002.
2. Slotnick, S.D., Moo, L.R., Kraut, M.A., Lesser, R.P., **Hart, J., Jr.** (2002). Interactions between thalamic and cortical rhythms during semantic memory recall in human. *Proceedings of the National Academy of Sciences USA, 99*(9), 6440-6443. PMCID: PMC122967.
3. **Hart, J., Jr.**, Gordon, B. (1992). Neural subsystems for object knowledge. *Nature, 359*(6390), 60-64.
4. **Hart, J., Jr,**, Berndt, R.S., Caramazza, A. (1985). Category-specific naming deficit following cerebral infarction. *Nature, 316*(6027), 439-440.

B. Positions and Honors

1979	Psychology Departmental Honors, The Johns Hopkins University
1982	Dean's Fellowship for Research, University of Maryland School of Medicine
1983	The William Alexander Hammond Award for Excellence in Neurology, Univ of MD SOM
1990-1993	Research Associate, Dept. of Neurology, The Johns Hopkins School of Medicine
1990-2001	Associate Member, The Zanvyl Krieger Mind/Brain Institute, The Johns Hopkins University
1993-2001	Assistant Professor, Department of Neurology, The Johns Hopkins School of Medicine
1996-2001	Assistant Professor (joint appointment), Dept of Cognitive Science, The Johns Hopkins Univ
1997-2001	Neurology Staff, The Johns Hopkins Hospital
1998-2001	Deputy Director, Division of Cognitive Neurology and Neuropsychology, Department of Neurology, The Johns Hopkins University; Chairman, Protocol review Committee, F.M. Kirby Research Center for Functional Brain Imaging, Kennedy Krieger Institute
2001-2005	Assoc. Prof., Depts. of Geriatrics, Neurology, and Radiology; Director, Laboratory of Cognition and Brain Imaging, Donald W. Reynolds Center on Aging, Univ. of AR for Medical Sciences
2002-2005	Staff Physician; Physician Researcher, GRECC; Director of the Geriatric Memory Disorders Clinic, Central Arkansas Veterans Healthcare System
2003-2005	Associate Professor, Department of Audiology and Speech Pathology, College of Health Related Professions, University of Arkansas for Medical Sciences
2004-2005	Associate Director, Clinical Programs and Evaluation, GRECC of CAVHS

2005-present Center for BrainHealth Medical Science Director; Jane and Bud Smith Distinguished Chair; Distinguished Chair in Neuroscience; Professor of Behavioral and Brain Sciences, UT Dallas
2006-present Professor, Departments of Neurology and Psychiatry, UT Southwestern Medical Center
2010-present Graduate School Faculty, Clinical Psychology Program, UT Southwestern Medical Center
2015-present Co-Director, Clinical Core, Alzheimer's Disease Center, UT Southwestern Medical Center

C. Contribution to Science

1. My initial studies established the categorical organization to knowledge in language (Hart et al., 1985) and in the visual system (Hart & Gordon, 1992). The initial study demonstrated a clear anomia for fruits and vegetables in a man with intact recognition of these and all other objects, leading to the concept of a categorical organization to lexical semantics. The second case was of a woman with anomia for animals but also an inability to verbally report the visual perceptual properties only of animals. These findings also established a more discrete unit to knowledge storage in the semantic system in the brain in that we were able to isolate category-feature units and that there were multiple semantic subsystems for knowledge in the brain (Figure 1). Up to this point, there had been no studies that demonstrated the categorical or featural organization to semantic memory, or that knowledge in the brain was not organized into multiple subsystems by which thought occurs but had been proposed to occur in one amodal system.

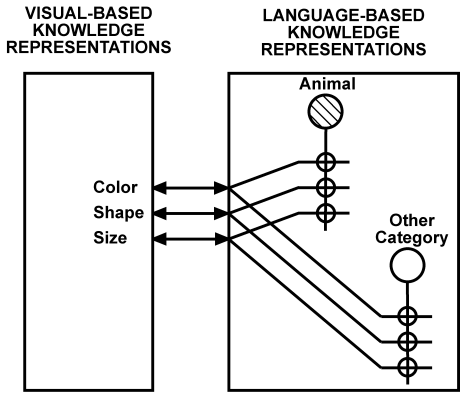


Figure 1. Separation of visual and verbal semantic systems as demonstrated by a patient with impaired naming of animals and their visual perceptual features.

a. Kraut, M.A., Moo, L.R., Segal, J.B., **Hart, J., Jr.** (2002). Neural activation during an explicit categorization task: category- or feature-specific effects? *Cognitive Brain Research, 13*(2), 213-220.
b. Deibert, E., Kraut, M., Kremen, S., **Hart, J., Jr.** (1999). Neural pathways in tactile object recognition. *Neurology, 52*(7), 1413-1417.
c. **Hart, J., Jr.**, Gordon, B. (1992). Neural subsystems for object knowledge. *Nature, 359*(6390), 60-64.
d. **Hart, J., Jr.**, Berndt, R.S., Caramazza, A. (1985). Category-specific naming deficit following cerebral infarction. *Nature, 316*(6027), 439-440.

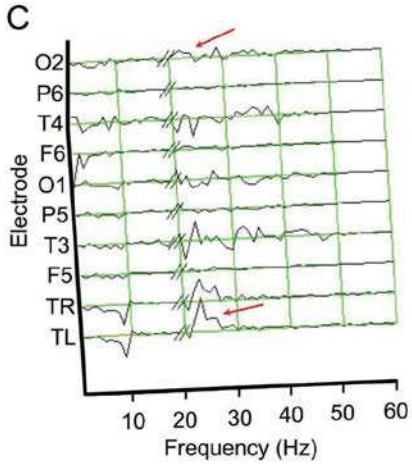


Figure 2. Graph showing the observed increase 25 Hz in the thalamic (TR, TL) and occipital electrode (O2) (red arrows) during correct retrievals.

2. I next approached the problem of how are these separate featural units combined together to form an integrated memory (Slotnick et al., 2002). We recorded electrical activity through thalamic depth and a limited montage of scalp electrodes as a patient performed the task of deciding whether two features that were presented combined to activate the memory of a single object ('humps' and 'desert' → 'camel'). On successful retrieval trials only, there was an increase in thalamic 25 Hz power ($p < .01$; Figure 2) (Slotnick et al., 2002). Of all scalp electrodes, only O2 showed a significant increase within this frequency band and response epoch ($p < .05$) (Figure 2). This high beta band power increase over occipital cortex correlated with the inferior temporo-occipital (visual memory) fMRI signal change during retrieval.

I proposed that 25 Hz rhythm mediated through the thalamus co-activates the neural representations of the features of the object memory, with the neural substrates of these representations oscillating in synchrony at 25 Hz. This synchronous co-activation of the features in the multiple representational subsystems signifies the multi-modal memory representation. Subsequently, we have performed the same study with normal controls using scalp EEG recording and found the same 25 Hz increase for retrievals compared to non-retrievals (Ferree et al., 2009), but in this instance, it was located in the electrodes over the region covering pre-SMA. (This area was not covered by scalp electrodes in the patient with thalamic depth electrodes.)

a. Ferree, T.C., Brier, M.R., **Hart, J., Jr.**, Kraut, M.A. (2009). Space-time-frequency analysis of EEG data using within-subject statistical tests followed by sequential PCA. *NeuroImage. 45*(1), 109-121. doi: 10.1016/j.neuroimage.2008.09.020.

b. Slotnick, S.D., Moo, L.R., Kraut, M.A., Lesser, R.P., **Hart, J., Jr.** (2002). Interactions between thalamic and cortical rhythms during semantic memory recall in human. *Proceedings of the National Academy of Sciences USA, 99*(9), 6440-6443. PMCID: PMC122967.
c. Crone, N.E., Hao, L., **Hart, J., Jr.**, Boatman, D., Lesser, R.P., Irizarry, R., Gordon, B. (2001). Electrocorticographic gamma activity during word production in spoken and sign language. *Neurology, 57*(11), 2045-2053.
d. Hart, J., Jr., Crone, N.E., Lesser, R.P., Sieracki, J., Miglioretti, D.L., Hall, C., Sherman, D., Gordon, B. (1998). Temporal dynamics of verbal object comprehension. *Proceedings of the National Academy of Sciences USA, 95*(11), 6498-6503. PMCID: PMC27830.

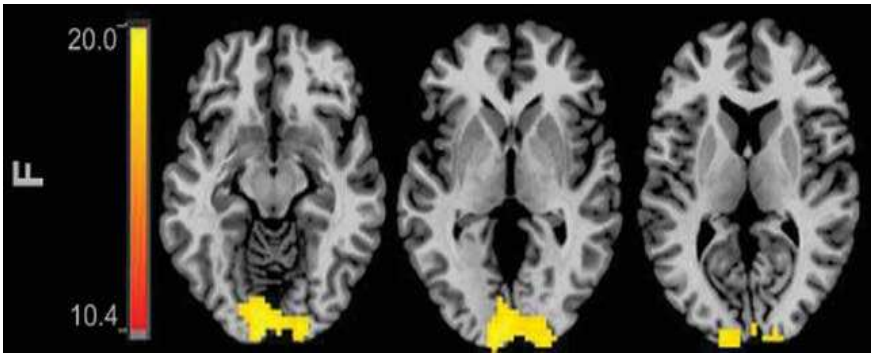


Figure 3. The main effect of threatening stimuli. Foci of signal change in the three axial images show regions of increased activation for threatening compared to pleasant stimuli in the visual association cortices in normal controls.

3. I then assessed how other features are linked to object memory that were part of different semantic subsystems with one being the emotional system. We used fMRI to identify anatomic regions engaged in detecting visually threatening and pleasant stimuli across multiple categories – animals, natural scenes, people in threatening and in nonthreatening situations, weapons and fruit & vegetables. These visual stimuli were visually-scrambled to create an image that does not represent a "real" item. The nonreal items comprised the same spatial frequency and color content as their corresponding real item. The subject's task was to determine whether the stimulus represented a real item. Our results demonstrated significant signal changes in visual association cortex (Brodmann [BA] 18 and 19) for threatening stimuli (Figure 3). We also detected an additional region that was more activated for manmade-threatening items than for natural threatening items (Figure 4). These two regions were located more laterally and ventrally to the primary threat region. These results reveal that there are neural regions selective for threatening visual stimuli and an additional region selective foe man-made threatening stimuli. The study demonstrates that fMRI can be used to map subjects' responses to threatening stimuli, including a selective region for man-made (including war-related and weapons) threatening stimuli. This technique, particularly with the isolation of a specific region associated with combat threats in the visual cortices is now being used as an objective marker for PTSD treatment response in our DOD study.

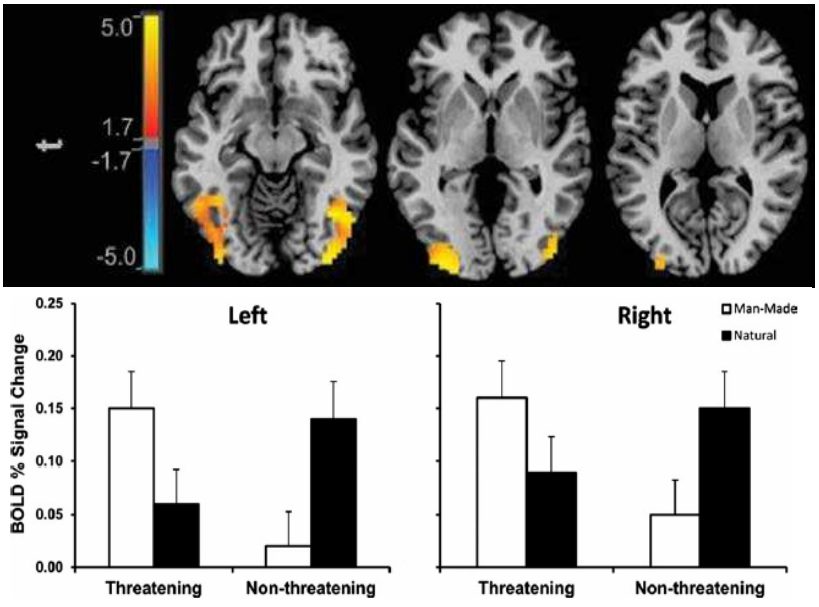


Figure 4. The top set of three axial images shows the significant interaction of increased activation for man-made threatening stimuli

a. DeLaRosa, B.L., Spence, J.S., Shakal, S.K., Motes, M.A., Calley, C.S., Calley, V.I., **Hart, J., Jr,**, Kraut, M.A. (2014). Electrophysiological spatiotemporal dynamics during implicit visual threat processing. *Brain and Cognition, 91*, 54-61. doi: 10.1016/j.bandc.2014.08.003.
b. Calley, C.S., Motes, M.A., Chiang, H.S., Buhl, V., Spence, J.S., Abdi, H., Anand, R., Maguire, M., Estevez, L., Briggs, R., Freeman, T., Kraut, M.A., **Hart, J., Jr.** (2013). Threat as a feature in visual semantic object memory. *Human Brain Mapping, 34*(8):1946-1955. doi: 10.1002/hbm.22039.
c. Kraut, M.A., Kremen, S., Moo, L.R., Segal, J.B., Calhoun, V., **Hart, J., Jr.** (2002). Object activation in semantic memory from visual multimodal feature input. *Journal of Cognitive Neuroscience, 14*(1), 37-47.

d. **Hart, J., Jr.**, Lesser, R.P., Gordon, B. (1992). Selective interference with the representation of size in the human by direct cortical electrical stimulation. *Journal of Cognitive Neuroscience, 4*(4), 337-344. doi: 10.1162/jocn.1992.4.4.337.

4. We used the task of features combining to aid in retrieving an object memory to assess a group of patients who reported a word retrieval problem – retired NFL players who were aging and developing this impairment (Hart et al., 2013). On further examination, a significant number of subjects had deficits in the word retrieval task, Boston Naming Test, and visual and verbal memory tests. On examining neuroimaging studies in the subjects, there was a significant correlation with white matter dysfunction and these cognitive deficits. We compared DTI Fractional Anisotropy (FA) measures between the groups of 14 athletes with cognitive impairment, 12 athletes without neurological problems, and age- and IQ-matched healthy controls (*N* = 26). We found reductions in FA throughout both cerebral hemispheres for the impaired NFL compared to the other two groups, with no significant difference between the non-impaired athletes and controls. Comparing cognitively impaired athletes and their matched controls (Figure 5), there were significant differences ($p < .05$, corrected), with lower FA in impaired athletes within middle and posterior corpus callosum and tracts extending to superior and inferior parietal lobules, which was more extensive in the left hemisphere. The findings support the notion that white matter disruption can affect memory retrieval circuits, evidenced in both word finding tasks and episodic memory tasks, and that this may be part of the pathological mechanisms involved in cognitive decline in individuals with a history of multiple concussions.

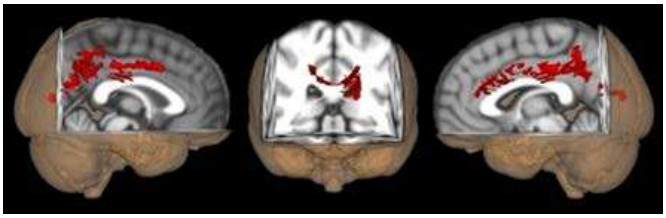


Figure 5. DTI voxel-wise analysis comparing FA differences between cognitively impaired, athletes (n = 10) and matched normal controls (n = 10). Red voxels indicate where FA is lower in the cognitively impaired athletes group than in

a. Strain, J.F., Womack, K.B., Didehbani, N., Spence, J.S., Conover, H., **Hart, J., Jr.**, Kraut, M.A., Cullum, C.M. (2015). Imaging Correlates of Memory and Concussion History in Retired National Football League Athletes. *JAMA Neurol.* Advance online publication. doi: 10.1001/jamaneurol.2015.0206.
b. Didehbani, N., Cullum, C.M., Mansinghani, S., Conover, H., **Hart, J., Jr.** (2013). Depressive symptoms and concussions in aging retired NFL players. *Archives of Clinical Neuropsychology, 28*(5), 418-24. doi: 10.1093/arclin/act028. PMCID: PMC4007104.
c. Strain, J., Didehbani, N., Cullum, C.M., Mansinghani, S., Conover, H., Kraut, M.A., **Hart, J., Jr.**, Womack, K.B. (2013). Depressive symptoms and white matter dysfunction in retired NFL players with concussion history. *Neurology, 81*(1), 25-32. doi: 10.1212/WNL.0b013e318299ccf8. PMCID: PMC3770203.
d. **Hart, J., Jr.**, Kraut, M.A., Womack, K.B., Strain, J., Didehbani, N., Bartz, E., Conover, H., Mansinghani, S., Lu, H., Cullum, C.M. (2013). Neuroimaging of cognitive dysfunction and depression in aging retired National Football League players: a cross-sectional study. *JAMA Neurology, 70*(3), 326-35. doi: 10.1001/2013.jamaneurol.340. PMCID: PMC4016798.

5. We combined the studies that we have performed over the years into a model of the neural circuitry of semantic object memory retrieval. We proposed a thalamo-cortical (pre-SMA)-caudate network as a retrieval circuit, and incorporated these findings into a hypothesized neural circuit for memory retrieval (see Figure 6) as part of the Neural Hybrid Model of semantic memory (Hart et al., 2013) that includes access to words. We propose that pre-SMA-thalamic interaction govern processes fundamental to semantic retrieval of an integrated object memory. At the onset of retrieval, pre-SMA initiates electrical interactions between multiple cortical regions associated with semantic memory subsystems'

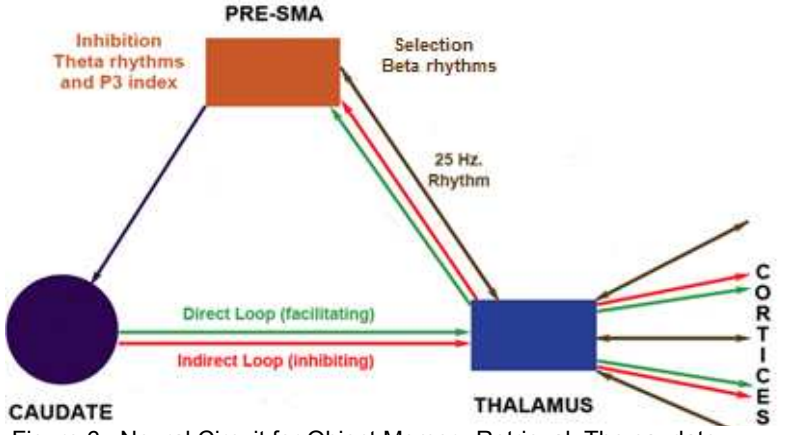


Figure 6. Neural Circuit for Object Memory Retrieval. The caudate functions to facilitate finding a correct vs incorrect target. Pre-SMA-thalamus circuit 25 Hz rhythm results in retrieval of the memory and word that signifies the memory. (Brown arrows signify 25 Hz. rhythms, red and green lines for connections involved in searching for correct retrievals and inhibiting incorrect retrievals.) The pre-SMA is engaged in selecting the correct object for retrieval which is reflected in 25 Hz beta rhythms and in inhibiting incorrect objects as indexed by 4 Hz theta frequency rhythms.

encoding. In our previous work, this was indexed by an increase in theta-band EEG power starting between 100–150 ms after stimulus presentation and was sustained throughout the trial (Hart et al., 2013). We posit that this activity represents initiation and maintenance of the memory search. When the correct memory is retrieved, there is a high beta-band power increase, which reflects communication between pre-SMA and thalamus, and terminates the search due to selection of a retrieved memory from multiple semantic memory subsystems. This high beta signal is also detected in cortical regions encoding for memory representation components (O2 on EEG). Manifestations of the response selection and inhibition aspects of these operations inform what may be reflected in the high beta (25 Hz) and the theta (4 Hz) EEG power changes. This circuit is modulated by the caudate nuclei to facilitate correct, and suppress incorrect, target memories (Figure 6). Thus, our model features clear neuroanatomic and electrophysiological task-related correlates of memory retrieval.

a. **Hart, J., Jr,**, Maguire, M.J., Motes, M., Mudar, R.A., Chiang, H.S., Womack, K.B., Kraut, M.A. (2013). Semantic memory retrieval circuit: role of pre-SMA, caudate, and thalamus. *Brain & Language, 126*(1), 89-98. doi: 10.1016/j.bandl.2012.08.002.
b. Brier, M.R., Maguire, M.J., Tillman, G.D., **Hart, J., Jr.**, Kraut, M.A. (2008). Event-related potentials in semantic memory retrieval. *Journal of the International Neuropsychological Society, 14*(5):815-22. doi: 10.1017/S135561770808096X.
c. **Hart, J., Jr.**, Anand, R., Zoccoli, S., Maguire, M., Gamino, J., Tillman, G., King, R., Kraut, M.A. (2007). Neural substrates of semantic memory. *Journal of the International Neuropsychological Society, 13*(5), 865-880. Review.
d. Kraut, M.A., Calhoun, V., Pitcock, J.A., Cusick, C., **Hart, J., Jr.** (2003). Neural hybrid model of semantic object memory: implications from event-related timing using fMRI. *Journal of the International Neuropsychological Society, 9*(7), 1031-1040.

Complete List of Published Work in MyBibliography:
http://www.ncbi.nlm.nih.gov/sites/myncbi/john.hart.2/bibliography/40326989/public/?sort=date&direction=ascending.

D. Research Support

Ongoing Research Support

529-14-0084-0001 (Hart) Texas Health and Human Service Commission 12/1/2013 – 8/31/2016
Non-Pharmacological Treatment for Symptoms of PTSD
This project will test a novel, non-pharmacological treatment for Post-Traumatic Stress Disorder (PTSD) utilizing an emerging noninvasive neurological treatment, repetitive Transcranial Magnetic Stimulation (rTMS).

RG 5117-A-1 (Hart) National Multiple Sclerosis Society 4/1/2014 – 3/31/2017
Identifying and Characterizing Auditory Processing Disruptions in Multiple Sclerosis
This project's goal is to identify specific characteristics of auditory processing difficulty in MS, and find associations between specific patterns of disability and evidence of MS at key locations along the auditory and language processing streams.

Completed Research Support (within last 3 years)

W81XWH-11-1-0612 (Hart) Department of Defense / TATRC 8/15/2011 – 9/14/2012
Enhancing Soldier Performance and Brain Repair Using Virtual Reality Hapto-Robotic Training

5R01NS067015 (Lu) NIH/NINDS 8/1/2010 – 7/31/2014
Modulation of Brain Activity by Control of the Inspired Air

R15AG037971 (Jafari/Hart) NIH/NIA 9/30/2011 – 8/31/2014
Using Gate and Sway Biofeedback to Reduce Falls in the Elderly

C76-HF-19573 (Chapman) Dept. of Health and Human Services - HRSA 9/1/2010 – 8/31/2015
BrainHealth and Repair Project

W81XWH-1120132 (Hart) Department of Defense / CDMRP 5/1/2011 – 4/30/2015
Novel Treatment of Emotional Dysfunction in PTSD

RESOURCES

Follow the 398 application instructions in Part I, 4.7 Resources.

The Alzheimer's Disease Center (ADC) is one of 32 centers and repositories funded by the National Institute on Aging to evaluate patients and conduct scientific research into the cause(s) of Alzheimer's disease. At UT Southwestern Medical Center, an interdisciplinary research team pools its talents to study the nature of Alzheimer's disease from many vantage points. Research is ongoing, moving closer to improved diagnosis and caregiving techniques, medical intervention, etiology, and eventual cure. The ADC provides a thorough diagnostic evaluation of adult memory problems.

The ADC has a strong research focus and conducts studies on brain changes related to healthy aging, mild cognitive impairment, Alzheimer's, and other disorders. Faculty members at UT Southwestern have been awarded more than $700K in peer reviewed grants for pilot studies from the ADC and the Friends of the ADC. This investment has been enriched by 21-fold as pilot studies have led to federal or Alzheimer's Association grants totaling $15M. Progress in basic science funding for Alzheimer's disease has been a major objective for our ADC and ranks the UTSW ADC as one of the important Center's contributing to AD research. The ADC has more than 30 individuals conducting Alzheimer's Disease Clinical and Research Programs on faculty, and the Center is recognized nationally as one of the most productive – publishing in excess of 160 peer reviewed scientific papers, chapters, and editorials in the past two years.

The ADC is directed by Roger N. Rosenberg, M.D., Professor of Neurology and Neurotherapeutics and the Abe (Brunky), Morris and William Zale Distinguished Chair in Neurology. Deputy Director Perrie M. Adams, Ph.D., holder of the Margaret D. Harris Professorship in Alzheimer's Research and the Associate Dean for Special Projects, co-directs the ADC. The Clinical Core is headed by C. Munro Cullum, Ph.D., Professor of Psychiatry and Chief of the division of Psychology with John Hart, MD as Co-Director. Charles L. White III, M.D., Professor of Pathology, directs the Neuropathology Core for the ADC. Joan Reisch, Ph.D., Professor of Clinical Sciences, directs the Statistical and Data Management Core of the ADC. The Education and Outreach Core is directed by Mary Quiceno, M.D., Assistant Professor.

The Alzheimer's Disease Center continues to emphasize research into the biology of this disease; develop new data on potential new experimental therapies; care for patients with Alzheimer's disease and related disorders in the Memory Clinic; and provide comprehensive educational programs for patients, caregivers, their families and the community.

Having a Psychology Division situated within a major medical school setting affords many opportunities for psychologists to make important contributions to healthcare, education, and research. The Division of Psychology is primarily comprised of clinical psychologists with expertise in various specialty areas. Most faculty members are involved in clinical, educational, and research efforts, often in multidisciplinary settings. The licensed clinicians in the Division of Psychology provide state-of-the-art diagnostic and treatment services to in- and outpatients with acute and chronic illnesses at the ambulatory clinics and the hospitals across the UT Southwestern campus.

The Division Chief is C. Munro Cullum, Ph.D., who has an extensive clinical and research background in cognitive disorders and neuropsychology. Five faculty members have achieved ABPP diplomat status, five are fellows of the American Psychological Association (APA), and a number have leadership positions in local and national professional organizations. An important part of the Division of Psychology is our training program in Clinical Psychology. This includes a Ph.D. program and a clinical internship, both of which are approved by the APA. The program is based upon a clinician-researcher model that is designed to train students broadly in clinical psychology and to help prepare them for postdoctoral work, professional licensure, and careers in a variety of settings.

Program Director/Principal Investigator (Last, First, Middle): Rosenberg, Roger

CHECKLIST

TYPE OF APPLICATION *(Check all that apply.)*

☒ NEW application. *(This application is being submitted to the PHS for the first time.)*

☐ RESUBMISSION of application number: _____
(This application replaces a prior unfunded version of a new, renewal, or revision application.)

☐ RENEWAL of grant number: _____
(This application is to extend a funded grant beyond its current project period.)

☐ REVISION to grant number: _____
(This application is for additional funds to supplement a currently funded grant.)

☐ CHANGE of program director/principal investigator.

Name of former program director/principal investigator: _____

☐ CHANGE of Grantee Institution. Name of former institution: _____

☐ FOREIGN application ☐ Domestic Grant with foreign involvement List Country(ies) Involved:

INVENTIONS AND PATENTS *(Renewal appl. only)* ☐ No ☐ Yes

If "Yes," ☐ Previously reported ☐ Not previously reported

1. PROGRAM INCOME ***(See instructions.)***
All applications must indicate whether program income is anticipated during the period(s) for which grant support is request. If program income is anticipated, use the format below to reflect the amount and source(s).

Budget Period	Anticipated Amount	Source(s)

2. ASSURANCES/CERTIFICATIONS ***(See instructions.)***
In signing the application Face Page, the authorized organizational representative agrees to comply with the policies, assurances and/or certifications listed in the application instructions when applicable. Descriptions of individual assurances/certifications are provided in Part III and listed in Part I, 4.1 under Item 14. If unable to certify compliance, where applicable, provide an explanation and place it after this page.

3. FACILITIES AND ADMINSTRATIVE COSTS (F&A)/ INDIRECT COSTS. See specific instructions.

☒ DHHS Agreement dated: 7/24/2012 ☐ No Facilities And Administrative Costs Requested.

☐ DHHS Agreement being negotiated with _____ Regional Office.

☐ No DHHS Agreement, but rate established with _____ Date _____

CALCULATION* *(The entire grant application, including the Checklist, will be reproduced and provided to peer reviewers as confidential information.)*

a. Initial budget period:	Amount of base $	15,182	x Rate applied	53.00%	% = F&A costs	$	8,046
b. 02 year	Amount of base $	15,537	x Rate applied	53.00%	% = F&A costs	$	8,235
c. 03 year	Amount of base $		x Rate applied	0.00%	% = F&A costs	$	
d. 04 year	Amount of base $		x Rate applied	0.00%	% = F&A costs	$	
e. 05 year	Amount of base $		x Rate applied	0.00%	% = F&A costs	$	
					TOTAL F&A Costs	$	16,281

*Check appropriate box(es):

☐ Salary and wages base ☒ Modified total direct cost base ☐ Other base *(Explain)*

☐ Off-site, other special rate, or more than one rate involved *(Explain)*

Explanation *(Attach separate sheet, if necessary.):*

4. DISCLOSURE PERMISSION STATEMENT: If this application does not result in an award, is the Government permitted to disclose the title of your proposed project, and the name, address, telephone number and e-mail address of the official signing for the applicant organization, to organizations that may be interested in contacting you for further information (e.g., possible collaborations, investment)? ☒ Yes ☐ No

UT SOUTHWESTERN
MEDICAL CENTER

DIRECTOR
Roger N. Rosenberg, M.D.
Professor of Neurology and Physiology
Department of Neurology and Neurotherapeutics
Abe (Brunky) Morris, and
William Zale Distinguished Chair in Neurology
214-648-3239 FAX 214-648-6824

ASSOCIATE DIRECTOR
Perrie M. Adams, Ph.D.
Professor of Psychiatry
Associate Dean for Research
Margaret D. Harris Professor in Alzheimer's Research
214-648-8545 FAX 214-648-8805

ADMINISTRATOR
Barbara A. Davis, M.A., L.P.C.
Department of Neurology and Neurotherapeutics
214-648-9367 FAX 214-648-9334

LEADER, CLINICAL CORE
C. Munro Cullum, Ph.D.
Professor of Psychiatry
Professor of Neurology and Neurotherapeutics
Director, Neuropsychology
Pam Blumenthal Distinguished Professor
of Clinical Psychology
214-648-5270 FAX 214-648-5297

LEADER, NEUROPATHOLOGY CORE
Charles L. White, III, M.D.
Professor of Pathology
Nancy R. McCune Distinguished Chair
in Alzheimer's Disease Research
Director, Division of Neuropathology
Director, Winspear Family Center for Research
on the Neuropathology of Alzheimer's Disease
214-648-2148 FAX 214-648-6325

LEADER, STATISTICS AND DATA MANAGEMENT CORE
Joan S. Reisch, Ph.D.
Professor of Biostatistics
Chief, Division of Biostatistics
Department of Clinical Sciences
214-648-2028 FAX 214-648-7673

LEADER, EDUCATION & INFORMATION CORE
Mary Ellen Quiceno, M.D.
Assistant Professor
Director, Cognitive and Memory Disorders Clinic
Department of Neurology and Neurotherapeutics
214-645-8800 FAX 214-648-2031

LEADER, NATIVE AMERICAN SATELLITE DIAGNOSTIC
AND TREATMENT CORE
Kyle B. Womack, M.D.
Assistant Professor
Department of Neurology and Neurotherapeutics
214-645-8800 FAX 214-648-2031

January 15, 2016

Alzheimer's Disease Center
Memory Research Unit

Walter A. Kukull, PhD
National Alzheimer's Coordinating Center
University of Washington
4311 11th Ave NE Ste 300
Seattle, WA 98105

Dear Bud:

I am writing to express my support for the collaborative grant titled "Plasma Markers of Lewy Body Disease", which is being submitted for funding by the National Alzheimer's Coordinating Center.

As the Director of the Alzheimer's Disease Center, I am endorsing the participation of our Center in this project under the direction of Sid O 'Bryant, PhD.

All key personnel associated with this project at our Center have received appropriate DHHS approved training in human subjects research.

We are pleased to contribute to an increased understanding of this important topic, and we look forward to participating in a scientifically productive project.

Sincerely,

Roger N. Rosenberg, MD

Department of Health and Human Services
Public Health Services

Grant Application

Do not exceed character length restrictions indicated.

LEAVE BLANK—FOR PHS USE ONLY.

Type	Activity	Number
Review Group		Formerly
Council/Board (Month, Year)		Date Received

1. TITLE OF PROJECT *(Do not exceed 81 characters, including spaces and punctuation.)*

Plasma biomarkers in Lewy Body Disease

2. RESPONSE TO SPECIFIC REQUEST FOR APPLICATIONS OR PROGRAM ANNOUNCEMENT OR SOLICITATION ☐ NO ☐ YES
(If "Yes," state number and title)

Number: NACC2016-COLLAB Title: NACC-funded Collaborative Projects, FY2016

3. PROGRAM DIRECTOR/PRINCIPAL INVESTIGATOR

3a. NAME (Last, first, middle)	3b. DEGREE(S)	3h. eRA Commons User Name
Montine, Thomas J	MD, PhD	tmontine

3c. POSITION TITLE
Alvord Professor and Chair

3d. MAILING ADDRESS *(Street, city, state, zip code)*
1959 NE Pacific Street
Seattle, WA 98195

3e. DEPARTMENT, SERVICE, LABORATORY, OR EQUIVALENT
Pathology

3f. MAJOR SUBDIVISION
School of Medicine

3g. TELEPHONE AND FAX *(Area code, number and extension)*
TEL: 206-543-1140 FAX: 206-744-8240

E-MAIL ADDRESS:
tmontine@uw.edu

4. HUMAN SUBJECTS RESEARCH	4a. Research Exempt	If "Yes," Exemption No.
☐ No ☒ Yes	☒ No ☐ Yes	

4b. Federal-Wide Assurance No.	4c. Clinical Trial	4d. NIH-defined Phase III Clinical Trial
00006878	☒ No ☐ Yes	☒ No ☐ Yes

5. VERTEBRATE ANIMALS ☒ No ☐ Yes — 5a. Animal Welfare Assurance No

6. DATES OF PROPOSED PERIOD OF SUPPORT *(month, day, year—MM/DD/YY)*		7. COSTS REQUESTED FOR INITIAL BUDGET PERIOD		8. COSTS REQUESTED FOR PROPOSED PERIOD OF SUPPORT	
From	Through	7a. Direct Costs ($)	7b. Total Costs ($)	8a. Direct Costs ($)	8b. Total Costs ($)
07/01/16	06/30/18	$18,651	$23,500	$37,302	$47,000

9. APPLICANT ORGANIZATION
Name University of Washington
Address
4333 Brooklyn Ave NE, Box 359472
Seattle, WA 98195-9472

10. TYPE OF ORGANIZATION
Public: → ☐ Federal ☒ State ☐ Local
Private: → ☐ Private Nonprofit
For-profit: → ☐ General ☐ Small Business
☐ Woman-owned ☐ Socially and Economically Disadvantaged

11. ENTITY IDENTIFICATION NUMBER
916001537
DUNS NO.605799469 Cong. District WA-007

12. ADMINISTRATIVE OFFICIAL TO BE NOTIFIED IF AWARD IS MADE
Name Amanda C. Snyder
Title Acting Co-Director, Office of Sponsored Programs
Address 4333 Brooklyn Ave NE, Box 359472
Seattle, WA 98195-9472
Tel: 206-543-4043 FAX: 206-685-1732
E-Mail: osp@uw.edu

13. OFFICIAL SIGNING FOR APPLICANT ORGANIZATION
Name Amanda C. Snyder
Title Acting Co-Director, Office of Sponsored Prog.
Address 4333 Brooklyn Ave NE, Box 359472
Seattle, WA 98195-9472
Tel: 206-543-4043 FAX: 206-768-1732
E-Mail: osp@uw.edu

14. APPLICANT ORGANIZATION CERTIFICATION AND ACCEPTANCE: I certify that the statements herein are true, complete and accurate to the best of my knowledge, and accept the obligation to comply with Public Health Services terms and conditions if a grant is awarded as a result of this application. I am aware that any false, fictitious, or fraudulent statements or claims may subject me to criminal, civil, or administrative penalties.

SIGNATURE OF OFFICIAL NAMED IN 13.
(In ink. "Per" signature not acceptable.)

DATE
12/31/15

Use only if preparing an application with Multiple PDs/PIs. See http://grants.nih.gov/grants/multi_pi/index.htm for details.

Contact Program Director/Principal Investigator (Last, First, Middle): Montine, Thomas J

3. PROGRAM DIRECTOR / PRINCIPAL INVESTIGATOR

3a. NAME (Last, first, middle)	3b. DEGREE(S)	3h. NIH Commons User Name
Tsuang, Debby W	MD, MSc	dtsuang

3c. POSITION TITLE
Professor

3d. MAILING ADDRESS *(Street, city, state, zip code)*
VAPS 182 GRECC
1660 S Columbian Way
Seattle, WA 98108

3e. DEPARTMENT, SERVICE, LABORATORY, OR EQUIVALENT
Psychiatry & Behavioral Sciences

3f. MAJOR SUBDIVISION
School of Medicine

3g. TELEPHONE AND FAX *(Area code, number and extension)*
TEL: 206-277-1333 FAX: 206-768-5364

E-MAIL ADDRESS:
dwt1@uw.edu

3. PROGRAM DIRECTOR / PRINCIPAL INVESTIGATOR

3a. NAME (Last, first, middle)	3b. DEGREE(S)	3h. NIH Commons User Name

3c. POSITION TITLE

3d. MAILING ADDRESS *(Street, city, state, zip code)*

3e. DEPARTMENT, SERVICE, LABORATORY, OR EQUIVALENT

3f. MAJOR SUBDIVISION

3g. TELEPHONE AND FAX *(Area code, number and extension)*
TEL: FAX:

E-MAIL ADDRESS:

3. PROGRAM DIRECTOR / PRINCIPAL INVESTIGATOR

3a. NAME (Last, first, middle)	3b. DEGREE(S)	3h. NIH Commons User Name

3c. POSITION TITLE

3d. MAILING ADDRESS *(Street, city, state, zip code)*

3e. DEPARTMENT, SERVICE, LABORATORY, OR EQUIVALENT

3f. MAJOR SUBDIVISION

3g. TELEPHONE AND FAX *(Area code, number and extension)*
TEL: FAX:

E-MAIL ADDRESS:

3. PROGRAM DIRECTOR / PRINCIPAL INVESTIGATOR

3a. NAME (Last, first, middle)	3b. DEGREE(S)	3h. NIH Commons User Name

3c. POSITION TITLE

3d. MAILING ADDRESS *(Street, city, state, zip code)*

3e. DEPARTMENT, SERVICE, LABORATORY, OR EQUIVALENT

3f. MAJOR SUBDIVISION

3g. TELEPHONE AND FAX *(Area code, number and extension)*
TEL: FAX:

E-MAIL ADDRESS:

PROJECT SUMMARY (See instructions):

The purpose of this project is to collect the requisite data and build the necessary collaborative relationshipsto submit a grant for a large-scale prospective study of the utility of blood-based biomarkers in Lewy Body disease (LBD). The long-term goal of this line of research is the generation of blood-based profiles that have diagnostic, prognostic and theragnostic value in LBD. Given the rapidly growing elderly population, neurodegenerative dementias are a major public health problem. LBD is the 2nd most prevalent neurodegenerative dementia accounting for 15-20% of cases and is often misdiagnosed as Alzheimer's disease (AD). LBD is an -synuclein disorder that is characterized by Lewy Body and Lewy neurites in specific areas of the brain as well as acetylcholine neuronal degeneration. There is frequent AD and LBD overlap making the differential diagnosis between LBD and AD a significant problem in clinical practice. Additionally, there is an urgent need for methods to predict clinical course in LBD to design trials and monitor interventions. Based on preliminary findings it is our hypothesis that a blood-based biomarker profile can be accurate in detecting and distinguishing LBD from AD and controls. The Specific Aims of this project are as follows: Specific Aim 1 – Replicate our blood-based profile of LBD in a larger sample and Specific Aim 2 – To identify biologically-based subgroups in LBD.

RELEVANCE (See instructions):

Lewy body disease is hard to distinguish from Alzheimer disease because the pathologies overlap. Based on promising preliminary data this study evaluates if a blood based biomarker is able to able to have diagnostic, therapeutic and pathogenic use.

PROJECT/PERFORMANCE SITE(S) (if additional space is needed, use Project/Performance Site Format Page)

Project/Performance Site Primary Location			
Organizational Name: University of Washington			
DUNS: 605799469			
Street 1: 4333 Brooklyn Ave NE		Street 2: Box 359472	
City: Seattle	County: King		State: WA
Province:	Country:		Zip/Postal Code: 98195-9472
Project/Performance Site Congressional Districts: WA-007			

Additional Project/Performance Site Location			
Organizational Name: VA Puget Sound			
DUNS: 020232971			
Street 1: VAPS 182 GRECC		Street 2: 1660 S Columbian Way	
City: Seattle	County:		State: WA
Province:	Country:		Zip/Postal Code: 98108
Project/Performance Site Congressional Districts: WA-007			

SCIENTIFIC/KEY PERSONNEL. See instructions. *Use continuation pages as needed* to provide the required information in the format shown below. Start with Program Director(s)/Principal Investigator(s). List all other key personnel in alphabetical order, last name first.

Name	eRA Commons User Name	Organization	Role on Project
Thomas J Montine	tmontine	UW	PI
Debby W Tsuang	dtsuang	UW / VA / SIBCR	Site PI
Cyrus Zabetian	czabetian	UW / VA / SIBCR	Co-Investigator

OTHER SIGNIFICANT CONTRIBUTORS

Name	Organization	Role on Project

Human Embryonic Stem Cells ☒ **No** ☐ **Yes**

If the proposed project involves human embryonic stem cells, list below the registration number of the specific cell line(s) from the following list: http://stemcells.nih.gov/research/registry/eligibilityCriteria.asp. *Use continuation pages as needed.*

If a specific line cannot be referenced at this time, include a statement that one from the Registry will be used.

Cell Line

Program Director/Principal Investigator (Last, First, Middle): Montine, Thomas J

DETAILED BUDGET FOR INITIAL BUDGET PERIOD DIRECT COSTS ONLY	FROM 7/1/16	THROUGH 6/30/17

List PERSONNEL *(Applicant organization only)*
Use Cal, Acad, or Summer to Enter Months Devoted to Project
Enter Dollar Amounts Requested *(omit cents)* for Salary Requested and Fringe Benefits

NAME	ROLE ON PROJECT	Cal. Mnths	Acad. Mnths	Summer Mnths	INST.BASE SALARY	SALARY REQUESTED	FRINGE BENEFITS	TOTAL
Thomas Montine	PD/PI	0			0	0	0	
Debby Tsuang	Site PI	0.12			183,300	1,833	445	2,278
Cyrus Zabetian	Co-Invest.	0.12			0	0	0	
James O'Connell	Study Coord	1.54			91,440	11,745	4,628	16,373
SUBTOTALS →						13,578	5,073	18,651

CONSULTANT COSTS	
EQUIPMENT *(Itemize)*	
SUPPLIES *(Itemize by category)*	
TRAVEL	
INPATIENT CARE COSTS	
OUTPATIENT CARE COSTS	
ALTERATIONS AND RENOVATIONS *(Itemize by category)*	
OTHER EXPENSES *(Itemize by category)*	

CONSORTIUM/CONTRACTUAL COSTS	DIRECT COSTS	
SUBTOTAL DIRECT COSTS FOR INITIAL BUDGET PERIOD *(Item 7a, Face Page)*		$ 18,651
CONSORTIUM/CONTRACTUAL COSTS	FACILITIES AND ADMINISTRATIVE COSTS	
TOTAL DIRECT COSTS FOR INITIAL BUDGET PERIOD		$ 18,651

BUDGET FOR ENTIRE PROPOSED PROJECT PERIOD
DIRECT COSTS ONLY

BUDGET CATEGORY TOTALS	INITIAL BUDGET PERIOD *(from Form Page 4)*	2nd ADDITIONAL YEAR OF SUPPORT REQUESTED	3rd ADDITIONAL YEAR OF SUPPORT REQUESTED	4th ADDITIONAL YEAR OF SUPPORT REQUESTED	5th ADDITIONAL YEAR OF SUPPORT REQUESTED
PERSONNEL: *Salary and fringe benefits. Applicant organization only.*	18,651	18,651			
CONSULTANT COSTS					
EQUIPMENT					
SUPPLIES					
TRAVEL					
INPATIENT CARE COSTS					
OUTPATIENT CARE COSTS					
ALTERATIONS AND RENOVATIONS					
OTHER EXPENSES					
DIRECT CONSORTIUM/ CONTRACTUAL COSTS					
SUBTOTAL DIRECT COSTS *(Sum = Item 8a, Face Page)*	18,651	18,651			
F&A CONSORTIUM/ CONTRACTUAL COSTS					
TOTAL DIRECT COSTS	18,651	18,651			

TOTAL DIRECT COSTS FOR ENTIRE PROPOSED PROJECT PERIOD	**$** 37,302

JUSTIFICATION. Follow the budget justification instructions exactly. Use continuation pages as needed.

Thomas J Montine, Center Director, 0.00 CM, Dr. Montine has been Director for the University of Washington Alzheimer's Disease Research Center (ADRC) since 2012 and Director of the Pacific Northwest Udall Center since 2010.

Debby Tsuang, MD, Site PI, 0.12 CM, Years 1-2, Dr. Tsuang is the Director of the Geriatric Research Education and Clinical Center (GRECC) at the VA Puget Sound Health Care System and professor in the department of psychiatry and behavioral sciences at the University of Washington. She has been an investigator in the UW ADRC for the past 20 years. She has served as the PI of numerous NIH and VA funded studies investigating the clinical, neuropathological and genetic characteristics of neurodegenerative disorders. Dr. Tsuang has 20+ years experience in the assessment and treatment of patients with AD, DLB and PDD. She will ensure that patients recruited into this study meet the current clinical diagnostic criteria. She will also train and supervise the study coordinator in the administration of the rating instruments.

Cyrus Zabetian, MD, Neurologist, 0.12 CM, Years 1-2 (no salary requested), Dr. Zabetian is an associate professor in the department of Neurology at the University of Washington and staff neurology at the VA Puget Sound in Seattle. He has served as PI on numerous studies on the genetics of Parkinson's disease. He also directs the Parkinson's Genetic Research Study (PaGeR) in Seattle, which has enrolled ~1,300 PD patients from the Pacific Northwest. Along with Dr. Tsuang, he will review detailed clinical assessments for patients with PD and DLB for this study. No salary support is requested; this research will be conducted as part of Dr. Raskind’s VA research duties.

James O’Connell, Study Coordinator, 1.54 CM, Years 1-2, Mr. O'Connell will help recruit and consent eligible subjects who are part of the UW Alzheimer's Disease Research Center or Pacific Northwest Udall Parkinson's Disease Research Center to participate in the proposed studies. He will help administer the additional clinical rating scales and informant based interviews. In addition, working with Center staff, he will collect and send blood to the coordinating center for blood based biomarker measurements. He will also ensure that clinical data be uploaded to the NACC via the ADRC's biostatistics and data core.

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FIVE PAGES.**

NAME: Thomas Jude Montine, M.D., Ph.D.

eRA COMMONS USER NAME (credential, e.g., agency login): tmontine

POSITION TITLE: Alvord Professor and Chair, Department of Pathology, Adjunct Professor of Neurological Surgery and of Neurology

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
Columbia University, New York, NY	B.A.	May 1983	Chemistry
University of Rochester, Rochester, NY	Ph.D.	Oct 1988	Pharmacology
McGill University, Montreal, Quebec	M.D.	June 1991	Medicine
Duke University, Durham, NC	Residency/ Fellowship	June 1995	Pathology/ Neuropathology

A. Personal Statement

The focus of my laboratory is the structural and molecular bases of cognitive impairment that occurs with advancing age, and how these processes promote Alzheimer's disease and Parkinson's disease. Our goal is to define key pathogenic steps through fundamental and clinical research, and thereby identify new potential therapeutic targets to protect cognitive function. My laboratory addresses these prevalent medical problems through a combination of epidemiology-neuropathology, genomics-neuropathology, biomarkers for clinical investigation and clinical trials, and experimental studies that test hypotheses concerning neuroprotection from free radical injury and innate immune activation in specific regions of brain. I have been Director for the University of Washington Alzheimer's Disease Research Center (ADRC) since 2012 and Director of the Pacific Northwest Udall Center since 2010.

B. Positions and Honors

Positions

1996–2002	Assistant and Associate Professor of Pathology, Vanderbilt Univ., Nashville, TN
2002–present	Alvord Endowed Chair and Professor of Pathology, University of Washington, Seattle, WA
2003–present	Adjunct Professor of Neurology, Oregon Health and Science University, Portland, OR
2010–present	Chair, Department of Pathology, University of Washington, Seattle, WA

Honors

1991	University Scholar, Graduating Class of 1991, McGill University
1991	Hewlett-Packard Award for Academic Excellence, graduating class, McGill University
1994	Korey Research Fellow Award, XII International Congress of Neuropathology
1996	American Society of Investigational Pathologists (FASEB), Merit Award
1997–2003	Editorial Board, *Journal of Neuropathology and Experimental Neurology*
1999–2006	NIH Scientific Review Panel, Molecular Neuropharmacology (MDCN-5)
2000–2002	Margaret and George Thorne Professorship in Pathology, Vanderbilt University
2002–present	Nancy and Buster Alvord Endowed Chair in Neuropathology, University of Washington
2004–2013	Editorial Board, *The American Journal of Pathology*
2006–2013	Senior Editor, *Brain Pathology*
2009–2013	Member, NIEHS Review Committee

2010–2015 Member, NIA-N Review Committee
2013 Chair, Udall Center Coordinating Committee
2013 Scientific Chair, NINDS/NIA: Alzheimer's Disease-Related Dementias conference
2014 Scientific Chair, NINDS: Parkinson's Disease 2014 conference
2015 President, American Association of Neuropathologists

C. Contribution to Science

Biomarkers: My laboratory has been contributing to biomarkers of neurodegenerative disease since the mid-1990's through a focus on advanced analytical methods and detection of pre-clinical pathophysiologic processes.

- **Montine TJ**, Markesbery WR, Morrow JD, Roberts LJ. Cerebrospinal fluid F_2-isoprostane levels are increased in Alzheimer's disease. *Annals of Neurology* 1998; 44:410-413.
- Li G, Sokal I, Quinn JF, Leverenz JB, Brodey M, Schellenberg GD, Kaye JA, Raskind MA, Zhang J, Peskind ER, **Montine TJ**. CSF tau/Aβ_{42} ratio for increased risk of mild cognitive impairment: a follow-up study. *Neurology* 2007; 69:631-639.
- Shi, M, Bradner J, Hancock AM, Chung KA, Quinn JF, Peskind ER, Galasko D, Jankovic J, Zabetian CP, Kim HM, Leverenz JB, **Montine, TJ**, Ginghina C, Kang UJ, Cain KC, Wang Y, Aasly J, Goldstein D, Zhang J. Cerebrospinal fluid biomarkers for Parkinson disease diagnosis and progression. *Annals of Neurology* 2011; 69:570-580. PMC3117674
- Li, G, Millard SP, Peskind ER, J Zhang J, CE Yu CE, Leverenz JB, Mayer C, Shofer JS, Raskind MA, Quinn JF, Galasko DR, **Montine TJ**. Cross-sectional and longitudinal relationships between cerebrospinal fluid biomarkers and cognitive function in people without cognitive impairment from across the adult life span *JAMA Neurology* 2014; 71:742-751. PMC4051849

Brain Aging and Neurodegeneration: In collaboration with colleagues across the US, I have focused on the structural and molecular changes that accompany human brain aging, how these are related to drug exposures, and mechanisms by which they may promote development of neurodegenerative disease.

- Sonnen JA, Larson EB, Crane PK, Haneuse S, Li G, Schellenberg GD, Craft S, Leverenz JB, **Montine TJ**. Pathological correlates of dementia in a longitudinal, population-based sample of aging. *Annals of Neurology* 2007; 62:406-413.
- Back SA, Kroenke CD, Sherman LS, Lawrence G, Gong X, Taber EN, Sonnen JA, Larson EB, **Montine TJ**. White matter lesions defined by diffusion tensor imaging in older adults. *Annals of Neurology* 2011; 70:465-476. PMC3177155
- Sonnen JA, Santa Cruz K, Hemmy LS, Woltjer R, Leverenz JB, Montine KS, Jack CR, Kaye J, Lim K, Larson EB, White L, **Montine TJ**. Ecology of the aging human brain. *Archives of Neurology* 2011; 68:1049-1056. PMC3218566
- Crane PK, Walker R, Hubbard RA, Li G, Nathan DM, Zheng H, Haneuse S, Craft S, **Montine TJ**, Kahn SE, McCormick W, McCurry SM, Bowen JD, Larson EB. Glucose levels and risk of dementia. *New England Journal of Medicine* 2013; 369:540-548. PMC3955123

Leadership in Neurodegenerative Disease Research: I have led or participated in several national and international consensus efforts in neurodegenerative disease focused on pre-clinical diagnosis, neuropathologic evaluation, and research priorities.

- Sperling RA, Aisen PS, Beckett LA, Bennett DA, Craft S, Fagan AM, Iwatsubo T, Jack CR, Jr, Kaye J, **Montine TJ**, Park DC, Reiman EM, Rowe CC, Siemers E, Stern Y, Yaffe K, Carrillo MC, Thies B, Morrison-Bogorad M, Wagster MV, Phelps CH. Toward defining the preclinical stages of Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. 2011. *Alzheimer's & Dementia: the journal of the Alzheimer's Association* 2011; 7:280-292. PMC3220946
- Hyman BT, Phelps CH, Beach TG, Bigio EH, Cairns NJ, Carrillo MC, Dickson DW, Duyckaerts C, Frosch MP, Masliah E, Mirra SS, Nelson PT, Schneider JA, Thal DR, Thies B, Trojanowski JQ, Vinters HV, **Montine TJ**. National Institute on Aging–Alzheimer's Association guidelines for the

neuropathologic assessment of Alzheimer's disease *Alzheimer's & Dementia: the journal of the Alzheimer's Association* 2012; 8:1-13. PMC3266529

- **Montine TJ**, Koroshetz WJ, Babcock D, Dickson DW, Galpern WR, Glymour MM, Greenberg SM, Hutton ML, Knopman DS, Kuzmichev AN, Manly JJ, Marder KS, Miller BL, Phelps CH, Seeley WW, Sieber BA, Silverberg NB, Sutherland M, Torborg CL, Waddy SP, Zlokovic BV, Corriveau RA. Recommendations of the Alzheimer's disease-related dementias conference. *Neurology* 2014; 83:851-860. PMC4155046
- Sieber BA, Landis S, Koroshetz W, Bateman R, Siderowf A, Galpern WR, Dunlop J, Finkbeiner S, Sutherland M, Wang H, Lee VM, Orr HT, Gwinn K, Ludwig K, Taylor A, Torborg C, **Montine TJ**. Prioritized research recommendations from the National Institute of Neurological Disorders and Stroke Parkinson's Disease 2014 conference. *Annals of Neurology* 2014; 76:469-472. PMC exempt (editorial)

Mechanisms of Injury and Therapeutics: Our work has focused on pathophysiologic mechanisms of neuron stress and injury in Alzheimer's and Parkinson's disease, mostly immune-mediated and oxidative injury, and strategies for suppressing their deleterious effects.

- Zhang J, Perry G, Smith MA, Robertson D, Olson SJ, Graham DG, **Montine TJ**. Parkinson's disease is associated with oxidative damage to cytoplasmic DNA and RNA in substantia nigra neurons. *American Journal of Pathology* 1999; 154:1423-1429.
- **Montine TJ**, Milatovic D, Gupta RC, Valyi-Nagy T, Morrow JD, Breyer RM. 2002. Neuronal oxidative damage from activated innate immunity is EP2 receptor–dependent. *Journal of Neurochemistry* 2002; 83:463-470.
- Liang X, Wang Q, Hand T, Wu L, Breyer RM, **Montine TJ**, Andreasson K. Deletion of the prostaglandin E_2 EP2 receptor reduces oxidative damage and amyloid burden in a model of Alzheimer's disease. *Journal of Neuroscience* 2005; 25:10180-10187.
- Li, X, Montine KS, CD Keene CD, **Montine TJ**. Different mechanisms of apolipoprotein E isoform–dependent modulation of prostaglandin E_2 production and triggering receptor expressed on myeloid cells 2 (TREM2) expression after innate immune activation of microglia. *FASEB Journal* 2015; Epub ahead of print. PMC journal - in process.

Neurogenetics: I am one of the founding Co-PIs of the Alzheimer's Disease Genetics Consortium (ADGC) and contribute to several other large consortia genetics projects focused on Alzheimer's disease, Parkinson's disease, and related disorders.

- Lambert JC, Ibrahim-Verbaas CA, Harold D, Naj AC, Sims R, Bellenguez C, DeStafano AL, et al., Meta-analysis of 74,046 individuals identifies 11 new susceptibility loci for Alzheimer's disease. *Nature Genetics* 2013; 45:1452-1458. PMC3896259
- Naj AC, Jun G, Beecham GW, Wang LS, Vardarajan BN, Buros J, Gallins PJ, Buxbaum JD, et al., Common variants at MS4A4/MS4A6E, CD2AP, CD33 and EPHA1 are associated with late-onset Alzheimer's disease. *Nature genetics* 2011; 43:436-441. PMC3090745
- Beecham GW, Hamilton K, Naj AC, Martin ER, Huentelman M, Myers AJ, Corneveaux JJ, Hardy J, Vonsattel JP, Younkin SG, Bennett DA, De Jager PL, Larson EB, Crane PK, Kamboh MI, Kofler JK, Mash DC, Duque L, Gilbert JR, Gwirtsman H, Buxbaum JD, Kramer P, Dickson DW, Farrer LA, Frosch MP, Ghetti B, Haines JL, Hyman BT, Kukull WA, Mayeux RP, Pericak-Vance MA, Schneider JA, Trojanowski JQ, Reiman EM, Schellenberg GD, **Montine TJ**. Genome-wide association meta-analysis of neuropathologic features of Alzheimer's disease and related dementias. *PLoS Genetics* 2014; 10:e1004606. PMC4154667
- Beecham GW, Dickson DW, Scott WK, Martin ER, Schellenberg G, Nuytemans K, Larson EB, Buxbaum JD, Trojanowski JQ, Van Deerlin VM, Hurtig HI, Mash DC, Beach TG, Troncoso JC, Pletnikova O, Frosch MP, Ghetti B, Foroud TM, Honig LS, Marder K, Vonsattel JP, Goldman SM, Vinters HV, Ross OA, Wszolek ZK, Wang L, Dykxhoorn DM, Pericak-Vance MA, **Montine TJ**, Leverenz JB, Dawson TM, Vance JM. PARK10 is a major locus for sporadic neuropathologically confirmed Parkinson disease. *Neurology* 2015; 84:972-980. PMC4352096

Complete list of published manuscripts available in PubMed by searching "montine t"

D. Research Support

Ongoing

P50 AG05136 (Thomas Montine) 05/01/05 - 04/30/15
"University of Washington Alzheimer's Disease Research Center"
Clinical, translational and, fundamental research into Alzheimer's disease with a focus on early detection and experimental therapeutics.
Role: PI of Center

P50 NS062684 (Thomas Montine) 08/01/09 - 07/31/15
"Udall Parkinson's Disease Center of Excellence"
The center has a three-fold mission: (i) Serve patients with PD, along with their caregivers and health care providers, (ii) Investigate and elucidate mechanisms that underlie cognitive impairment in PD, and (iii) Create new knowledge and generate novel resources for clinical, translational, and basic research to be shared with the community of scientists investigating PD
Role: PI of Center

R01 AG031892 (Thomas Montine) 04/01/08 - 08/31/17
"White Matter Injury in Age-Related Cognitive Decline"
Our goal in this multisite, multicomponent R01 is to determine the biochemical and cellular mechanisms that underlie WM injury as detected with high field MRI.
Role: PI

R01 ES16754 (Thomas Montine) 07/01/09 - 06/30/15 (NCE)
"Toxicants and innate immunity in models of Parkinson's disease"
Our focus is PGE2 receptors, called EP1 through EP4, with the goal of developing new therapeutic targets for PD. We will use genetically altered mouse models combined with potentially relevant environmental toxicant models that mimic the central nervous system effects of peripheral endotoxin exposure.
Role: PI

R01 AG048232 (Katrin Andreasson and Thomas Montine) 09/01/14 - 06/30/19
"Targeting the kynurenine pathway in Alzheimer's disease"
Our goal is to determine whether increased tryptophan metabolism is mechanistically linked to development of AD and whether TDO2/IDO1 tryptophan metabolism can be targeted in prevention and treatment of AD.
Role: MPI

U01 AG046871 (Thomas Montine and Lon White) 04/01/13 - 03/31/16
"Neuropathologic research on dementia using Nun Study and HAAS data"
This project uses already-collected information and images of autopsy brain sections from the Nun Study and the Honolulu-Asia Aging Study to better understand the roles of amyloid plaques and neurofibrillary tangles, as well as brain atrophy, in the direct causation of cognitive decline and dementia. It will also use data from the same studies to assess the likely impact and utility of revised neuropathologic criteria.
Role: MPI

U01 AG046161 (Allan Levey et al) 09/01/14 - 04/30/19
"Discovery of novel proteomic targets for treatment of Alzheimer's disease"
The goal of this project is to use proteomics to better understand Alzheimer's disease pathogenesis with a large-scale, unbiased, and direct approach to discover and validate novel disease processes in postmortem AD brain, and to prioritize new targets for early stage therapeutic intervention.
Role: MPI

U01 AG32984 (Gerard Schellenberg) 04/01/09 - 04/30/15
"Alzheimer's Disease Genetic Consortium"
Large multicenter project that coordinates national effort to determine genetic associations to late-onset AD.
Role: Co-PI

U01 AG006781 (PI: Larson, Eric B) 09/30/09 - 08/31/15 (NCE)
"Alzheimer's Disease Patient Registry (ADPR)/Adult Changes in Thought (ACT) Study"

The major goals of this project are to determine environmental, life-style, and medical risk factors for cognitive impairment and dementia in in a community-based epidemiological study with neuropathologic endpoints.
Role: Co-Investigator

Completed (last 3 years)

U01 AG 016976 (Kukull) 07/01/99 – 06/30/19
"National Alzheimer's Coordinating Center (NACC)" *07/01/12 – 06/30/14 (Montine Project)*
NACC Collaborative Project "Optimization of Neuropathologic Assessment of Alzheimer's Disease"
The goal of this research is to fill this important gap in our knowledge by undertaking a collaborative study of neuropathologic assessment among 10 AD Centers.
Role: Team Leader

BIOGRAPHICAL SKETCH

Provide the following information for the key personnel and other significant contributors.
Follow this format for each person. DO NOT EXCEED FIVE PAGES.

NAME: **Tsuang, Debby W**

eRA COMMONS USER NAME: DTsuang

POSITION TITLE: Professor of Psychiatry and Behavioral Sciences and Adjunct Professor of Medical Genetics and Epidemiology

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	YEAR(s)	FIELD OF STUDY
University of Iowa	BS	1983	Psychology
University of Iowa College of Medicine	MD	1988	Medicine
University of Iowa College of Medicine	MSc	1992	Epidemiology
University of Iowa	Resident Physician	1992	Psychiatry
Geriatric Research, Education, and Clinical Center (GRECC), VA Puget Sound Health Care System	Fellowship	1995	Geriatric Psychiatry
University of Washington School of Medicine (UWSOM)	Fellowship	1995	Medical Genetics

A. Personal Statement

Over the past 20 years, my research has focused on the genetics of neurodegenerative disorders. Within this context, my recent work focuses on using innovative genomic technologies to elucidate the complex genetic architecture underlying dementia, particularly Alzheimer's disease (AD) and Lewy body dementias. I am the Director of the Geriatric Research, Education, and Clinical Center (GRECC), and I have served as co-PI of the clinical core of the Alzheimer's Disease Genetics Consortium (ADGC) since 2009. I am also the former Associate Director of the Clinical Core of the NIA-funded University of Washington Alzheimer's Disease Research Center (ADRC), and I have served as the primary VA Puget Sound referral from neurologists who treat dementia patients with treatment-resistant agitation or psychosis. In this role, I have trained young investigators in the evaluation of complex behavioral disorders, developed a comprehensive evaluation scheme and a psychosocial and medication-supported environment for my patients, and helped to better characterize the unique neuropathology of dementia with Lewy bodies (DLB). In these capacities, I have worked closely with Dr. Zabetian in the recruitment and clinical and biospecimen characterization of participants with neurodegenerative disorders like Parkinson's disease (PD) and DLB and then the characterization of the role that the *APOE* and *GBA* genetic risk factors play in these disorders. Given these experiences and my interest in DLB, I am well-prepared to lead the proposed studies at the UW and VA Puget Sound.

B. Positions and Honors

Positions and Employment

1993-1995 Acting Instructor, Dept of Psychiatry and Behavioral Sciences, University of Washington School of Medicine (UWSOM), Seattle, WA
1995-1999 Acting Assistant Professor, Dept of Psychiatry and Behavioral Sciences, UWSOM, Seattle, WA
1995-2004 Adjunct Assistant Professor, Dept Epidemiology, UW School of Public Health and Community Medicine (UWSPH), Seattle, WA
1999-2004 Assistant Professor Dept of Psychiatry and Behavioral Sciences, UWSOM, Seattle, WA
2004-2009 Associate Professor, Dept of Psychiatry and Behavioral Sciences, UWSOM, Seattle, WA
2004-2009 Adjunct Associate Professor, Dept Epidemiology, UWSPH, Seattle, WA
2007-2009 Adjunct Associate Professor, Div of Medical Genetics, Dept of Internal Medicine, UWSOM, Seattle, WA
2009- Professor, Dept of Psychiatry and Behavioral Sciences, UWSOM, Seattle, WA
2009- Adjunct Professor, Div of Medical Genetics, Dept of Internal Medicine, UWSOM, Seattle, WA
2009- Adjunct Professor, Department of Epidemiology, UWSOM, Seattle, WA
2011- Director, VISN-20 GRECC, Veterans Affairs Puget Sound Health Care System, Seattle, WA

Other Experience and Professional Memberships

2006-2009 Review Committee Member, NIMH Behavioral Genetics and Epidemiology Study Section
2006-2009 Program Planning Committee Member, Society of Biological Psychiatry

2007- Editorial Board, *Am J Med Genet (Neuropsychiatric Section)*
2006- Executive Steering Committee, Behavioral Neuroscience Group, VAPSHCS
2006- Committee Member, Dept of Psychiatry Research Task Force, University of Washington
2009- Committee Member, Scientific Review Committee, R&D, VAPSHCS
2001- Seattle Institute for Biomedical and Clinical Research

C. Contribution to Science

1. Dementia with Lewy bodies (DLB): I have initiated national collaborative studies that helped to identify and differentiate a subgroup of patients with DLB, a condition that falls between Alzheimer's disease (AD) and Parkinson's disease (PD). These patients have severe neuroleptic sensitivity and unique pathophysiological, biochemical, and clinical traits. In the first studies of their kind, my colleagues and I conducted systematic neuropathological studies in large samples of dementia cases from multiple ADRCs, systematically staining and evaluating over 600 neuropathological cases for the presence of AD and Lewy-related pathology (LRP). This work also clarified the relationship between DLB and the *APOE* gene (e.g., Tsuang et al., 2005 and Tsuang et al., 2013). My work has also investigated the hypothesis that Lewy body disorders may be heritable within families and may therefore be amenable to genetic dissection. In studying families with AD who have a single causative genetic mutation, my collaborators and I found significant variability in both the frequency and the distribution of LRP (e.g., Leverenz et al., 2006). This led to our current hypothesis that rather than functioning as a single-gene disorder, like some forms of AD, Lewy body dementias are instead the result of multiple genetic and/or environmental factors. In addition, I led studies that specifically examined cases with and without visual hallucinations and found that visual hallucinations are associated with LRP. The presence of LRP in patients presents a different clinical profile compared to patients with AD pathology alone (e.g., Tsuang et al., 2009).

   a. **Tsuang DW**, Wilson RK, Lopez OL, Luedecking-Zimmer EK, Leverenz JB, DeKosky ST, Kamboh MI, Hamilton RL. Genetic association between the APOE*4 allele and Lewy bodies in Alzheimer disease. Neurology. 2005; 64 (3):509-13. PMC1487185.
   b. Leverenz JB, Fishel MA, Peskind ER, Montine TJ, Nochlin D, Steinbart E, Raskind MA, Schellenberg GD, Bird TD, **Tsuang D**. Lewy body pathology in familial Alzheimer disease: evidence for disease- and mutation-specific pathologic phenotype. Arch Neurol. 2006; 63 (3):370-6. PMC1892620.
   c. **Tsuang D**, Larson EB, Bolen E, Thompson ML, Peskind E, Bowen J, McCormick W, Teri L, Kukull W, Vavrek D, Montine T, Leverenz JB. Visual hallucinations in dementia: a prospective community-based study with autopsy. Am J Geriatr Psychiatry. 2009; 17 (4):317-23. PMC2742470.
   d. **Tsuang D**, Leverenz JB, Lopez OL, Hamilton RL, Bennett DA, Schneider JA, Buchman AS, Larson EB, Crane PK, Kaye JA, Kramer P, Woltjer R, Trojanowski JQ, Weintraub D, Chen-Plotkin AS, Irwin DJ, Rick J, Schellenberg GD, Watson GS, Kukull W, Nelson PT, Jicha GA, Neltner JH, Galasko D, Masliah E, Quinn JF, Chung KA, Yearout D, Mata IF, Wan JY, Edwards KL, Montine TJ, Zabetian CP. APOE epsilon4 increases risk for dementia in pure synucleinopathies. JAMA Neurol. 2013; 70 (2):223-8. PMC3580799.

2. Alzheimer's disease (AD): As the Director of the GRECC and the former Associate Director of the UW ADRC Clinical Core, I have had the opportunity to assist my colleagues on early genetic studies of the relationship between *APOE* and AD (e.g., Tsuang et al., 1999), as well as studies that have explored the efficacy of statin treatment for AD in a variety of subject groups (e.g., Li et al., 2004). More recently, I have used my genetic and phenotyping expertise to contribute to large-scale international genetic studies of AD. As the PI of the ADGC Phenotyping Core, for example, I contributed to the analysis and collection of data that led to the confirmation of *CR1*, *CLU*, and *PICALM* as AD risk loci (Jun et al., 2010), and then, more recently, to the identification of 11 novel loci that may function as genetic risks for late-onset AD (Lambert et al., 2013).

   a. **Tsuang D**, Larson EB, Bowen J, McCormick W, Teri L, Nochlin D, Leverenz JB, Peskind ER, Lim A, Raskind MA, Thompson ML, Mirra SS, Gearing M, Schellenberg GD, Kukull W. The utility of apolipoprotein E genotyping in the diagnosis of Alzheimer disease in a community-based case series. Arch Neurol. 1999; 56 (12):1489-95. PMID10593304.
   b. Li G, Higdon R, Kukull WA, Peskind E, Van Valen Moore K, **Tsuang D**, van Belle G, McCormick W, Bowen JD, Teri L, Schellenberg GD, Larson EB. Statin therapy and risk of dementia in the elderly: a community-based prospective cohort study. Neurology. 2004; 63 (9):1624-8. PMID15534246.

c. Jun G, Naj AC, Beecham GW, Wang LS, Buros J, Gallins PJ, Buxbaum JD, Ertekin-Taner N, Fallin MD, Friedland R, Inzelberg R, Kramer P, Rogaeva E, St George-Hyslop P, Alzheimer's Disease Genetics Consortium, Cantwell LB, Dombroski BA, Saykin AJ, Reiman EM, Bennett DA, Morris JC, Lunetta KL, Martin ER, Montine TJ, Goate AM, Blacker D, **Tsuang DW**, Beekly D, Cupples LA, Hakonarson H, Kukull W, Foroud TM, Haines J, Mayeux R, Farrer LA, Pericak-Vance MA, Schellenberg GD. Meta-analysis confirms CR1, CLU, and PICALM as Alzheimer disease risk loci and reveals interactions with APOE genotypes. Arch Neurol. 2010; 67 (12):1473-84. PMC3048805.

d. Lambert JC, Ibrahim-Verbaas CA, Harold D, Naj AC, Sims R, Bellenguez C, DeStafano AL, Bis JC, Beecham GW, Grenier-Boley B, Russo G, Thorton-Wells TA, Jones N, Smith AV, Chouraki V, Thomas C, Ikram MA, Zelenika D, Vardarajan BN, Kamatani Y, Lin CF, Gerrish A, Schmidt H, Kunkle B, Dunstan ML, Ruiz A, Bihoreau MT, Choi SH, Reitz C, Pasquier F, Cruchaga C, Craig D, Amin N, Berr C, Lopez OL, De Jager PL, Deramecourt V, Johnston JA, Evans D, Lovestone S, Letenneur L, Moron FJ, Rubinsztein DC, Eiriksdottir G, Sleegers K, Goate AM, Fievet N, Huentelman MW, Gill M, Brown K, Kamboh MI, Keller L, Barberger-Gateau P, McGuiness B, Larson EB, Green R, Myers AJ, Dufouil C, Todd S, Wallon D, Love S, Rogaeva E, Gallacher J, St George-Hyslop P, Clarimon J, Lleo A, Bayer A, **Tsuang DW**, Yu L, Tsolaki M, Bossu P, Spalletta G, Proitsi P, Collinge J, Sorbi S, Sanchez-Garcia F, Fox NC, Hardy J, Deniz Naranjo MC, Bosco P, Clarke R, Brayne C, Galimberti D, Mancuso M, Matthews F, European Alzheimer's Disease I, Genetic, Environmental Risk in Alzheimer's D, Alzheimer's Disease Genetic C, Cohorts for H, Aging Research in Genomic E, Moebus S, Mecocci P, Del Zompo M, Maier W, Hampel H, Pilotto A, Bullido M, Panza F, Caffarra P, Nacmias B, Gilbert JR, Mayhaus M, Lannefelt L, Hakonarson H, Pichler S, Carrasquillo MM, Ingelsson M, Beekly D, Alvarez V, Zou F, Valladares O, Younkin SG, Coto E, Hamilton-Nelson KL, Gu W, Razquin C, Pastor P, Mateo I, Owen MJ, Faber KM, Jonsson PV, Combarros O, O'Donovan MC, Cantwell LB, Soininen H, Blacker D, Mead S, Mosley TH, Jr., Bennett DA, Harris TB, Fratiglioni L, Holmes C, de Bruijn RF, Passmore P, Montine TJ, Bettens K, Rotter JI, Brice A, Morgan K, Foroud TM, Kukull WA, Hannequin D, Powell JF, Nalls MA, Ritchie K, Lunetta KL, Kauwe JS, Boerwinkle E, Riemenschneider M, Boada M, Hiltuenen M, Martin ER, Schmidt R, Rujescu D, Wang LS, Dartigues JF, Mayeux R, Tzourio C, Hofman A, Nothen MM, Graff C, Psaty BM, Jones L, Haines JL, Holmans PA, Lathrop M, Pericak-Vance MA, Launer LJ, Farrer LA, van Duijn CM, Van Broeckhoven C, Moskvina V, Seshadri S, Williams J, Schellenberg GD, Amouyel P. Meta-analysis of 74,046 individuals identifies 11 new susceptibility loci for Alzheimer's disease. Nat Genet. 2013; 45 (12):1452-8. PMC3896259.

3. Parkinson's disease (PD): In collaboration with Dr. Zabetian, I have also helped to lead projects that sought to determine how genetic factors influence the risk of developing dementia in PD. This work has also examined the particular patterns of cognitive impairment seen in PD. Given my interest in the intersection of DLB, AD, and PD, we compared the variation of potentially pathogenic genes in autopsied subjects with PD with dementia (PDD), DLB, and no presence of neurodegeneration. We found that both *APOE* ε4 and *GBA* mutations substantially increase the risk for both DLB and PDD (e.g., Mata et al., 2008 and Tsuang et al., 2012). Additionally, when our sample was limited to cases with no or low levels of AD pathology (i.e., neuritic plaques and neurofibrillary tangles), *APOE* ε4 was still associated with PDD and DLB; this may suggest that apoE plays a role in neurodegeneration that is unrelated to amyloid processing (e.g., Tsuang 2013). In follow-up studies of our work with the *GBA* mutation, we identified impairment in working memory/executive function and visuospatial abilities that were uniquely associated with PD patients who harbored *GBA* mutations (e.g., Mata et al., 2015). These results represent a key step toward understanding the mechanisms underlying the heterogeneity of PD-related cognitive impairment.
   a. Mata IF, Samii A, Schneer SH, Roberts JW, Griffith A, Leis BC, Schellenberg GD, Sidransky E, Bird TD, Leverenz JB, **Tsuang D**, Zabetian CP. Glucocerebrosidase gene mutations: a risk factor for Lewy body disorders. Arch Neurol 2008; 65:379-382. PMC2826203.
   b. **Tsuang D**, Leverenz JB, Lopez OL, Hamilton RL, Bennett DA, Schneider JA, Buchman AS, Larson EB, Crane PK, Kaye JA, Kramer P, Woltjer R, Kukull W, Nelson PT, Jicha GA, Neltner JH, Galasko D, Masliah E, Trojanowski JQ, Schellenberg GD, Yearout D, Huston H, Fritts-Penniman A, Mata IF, Wan JY, Edwards KL, Montine TJ, Zabetian CP. GBA mutations increase risk for Lewy body disease with and without Alzheimer disease pathology. Neurology. 2012; 79 (19):1944-50. PMC3484986.
   c. **Tsuang D**, Leverenz JB, Lopez OL, Hamilton RL, Bennett DA, Schneider JA, Buchman AS, Larson EB, Crane PK, Kaye JA, Kramer P, Woltjer R, Trojanowski JQ, Weintraub D, Chen-Plotkin AS, Rick J, Irwin

D, Schellenberg GD, Watson GS, Kukull W, Nelson PT, Jicha GA, Neltner JH, Galasko D, Masliah E, Quinn JF, Chung KA, Yearout D, Mata IF, Wan JY, Edwards KL, Montine TJ, Zabetian CP. *APOE* ε4 increases risk for dementia in pure synucleinopathies. JAMA Neurol 2013; 70:223-228. PMC3580799.

d. Mata IF, Leverenz JB, Weintraub D, Trojanowski JQ, Chen-Plotkin A,Van Deerlin VM, Ritz B, Rausch R, Factor SA, Wood-Siverio C, Quinn JF, Chung KA, Peterson-Hiller AL, Goldman JG, Stebbins GT, Bernard B, Espay AJ, Revilla FJ, Devoto J, Rosenthal LS, Dawson TM, Albert MS, **Tsuang D**, Huston H, Yearout D, Hu SC, Cholerton BA, Montine TJ, Edwards KL, Zabetian CP. *GBA* variants are associated with a distinct pattern of cognitive deficits in Parkinson disease. Mov Disord; 2015. doi: 10.1002/mds.26359. [Epub ahead of print.] PMID 26296077.

Complete list of published work (128 peer-reviewed publications) here: http://tinyurl.com/kwk76z7

D. Research Support

Ongoing Research Support

U01 AG032984 Schellenberg (PI) 03/01/09-03/31/20
Alzheimer's Disease Genetics Consortium: Clinical case-control genome-wide association studies
This project will conduct genome-wide association studies in controls and neuropathologically confirmed cases with Alzheimer's disease (AD) to identify SNPs associated with AD.
Role: PI, Phenotyping Core

R01 AG041797 Mayeux (PI) 04/15/12-03/31/17
Epidemiology of familial late-onset Alzheimer's disease (LOAD)
This project seeks to show that genetic variants have a greater impact on LOAD risk and disease progression in multiplex families than in sporadic cases, as well as an effect on phenocopies and incomplete penetrance.
Role: Site PI

Department of Veterans Affairs Merit Review Tsuang (PI) 10/01/13-09/30/17
Deep Sequencing in Schizophrenia
This project seeks to identify rare genetic variants in high-density families with schizophrenia using next-generation sequencing technologies.
Role: PI

P50 AG005136 Montine (PI) 05/01/10-04/30/20
Alzheimer's Disease Research Center: Core B
This large multidisciplinary center aims to learn about the pathobiology of AD and to develop experimental therapies. Core B aims to characterize and evaluate patients with AD and matched controls for ADRC projects.
Role: Co-Investigator, Clinical Core

U01 AG049505 Seshadri (PI) 06/15/14-05/31/18
CHARGE: Identifying risk & protective single-nucleotide variants (SNV) for AD in ADSP case-control sample
This project will identify AD-related SNVs in CHARGE and ADSP whole-genome and -exome sequence data.
Role: Co-investigator

U01 AG049507 Wijsman (PI) 06/15/14-05/31/18
Sequence-based discovery of AD risk and protective alleles
This ADSP project seeks to identify SNVs and CNVs related to AD endophenotypes.
Role: Co-investigator

P50 NS062684 Montine (PI) 08/01/09-06/30/20
Pacific Northwest Udall Center (PANUC)
This project aims to identify genetic risks for cognitive impairment in PD, develop therapeutic targets, detect preclinical PD using brain imaging, and perform clinical trials on balance, gait, and cognitive impairment.
Role: Co-Investigator

Completed Research Support

R01 MH065558 Tsuang (PI) 04/01/10-03/31/14
Consortium on the Genetics of Endophenotypes and Schizophrenia
This project examined the genetics of intermediate phenotypes in schizophrenia to determine whether neurobiological deficits reflect common underlying heritable dysfunction in all schizophrenia patients.
Role: PI

Department of Veterans Affairs Merit Review Tsuang (PI) 10/01/08-09/30/13
Identification of CNVs in schizophrenia
This project sought to identify common schizophrenia-related CNVs using the Illumina 1M BeadChip array.
Role: PI

Department of Veterans Affairs Tsuang (PI) 07/01/2013
Shared Equipment Evaluation Program: Next-Generation Illumina Sequencing System
This grant acquired an Illumina Hi-Seq 2000 next-generation sequencer for the VISN-20 Genetics Core.
Role: PI

NARSAD Independent Investigator Award Tsuang (PI) 09/15/09-09/14/12
Deep sequencing in schizophrenia
This project used next-generation deep-sequencing methods to detect rare variants in schizophrenia exomes.
Role: PI

NIH/NINDS R01 NS48595 Montine (PI) 9/1/03–8/31/08
Characterization of DLB: A Collaborative Study
This project collected clinical and neuropathological material for over 500 subjects in order to investigate the clinical, neuropathological, and genetic characteristics of dementia with Lewy bodies.
Role: site PI

NIH/National Alzheimer's Disease Coordinating Center Pilot Collaborative Study
Tsuang (PI) 7/1/03–6/30/05
This pilot collaborative study initiated the infrastructure to collect and analyze clinical and neuropathological material for over 500 subjects, which facilitated the funding of the subsequent R01.
Role: Consortium PI

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FIVE PAGES.**

NAME: Cyrus Parse Zabetian, MD, MS

eRA COMMONS USER NAME (credential, e.g., agency login): Zabetian

POSITION TITLE: Associate Professor

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	YEAR(s)	FIELD OF STUDY
UCLA	B.S.	1982-1986	Biology
University of Washington	M.S.	1987-1988	Systematic Ichthyology
University of Hawaii		1988-1989	Marine Zoology
University of Pittsburgh		1989-1990	Medicine
University of Miami	M.D.	1990-1994	Medicine
American Board of Psychiatry and Neurology	Board Certification	2000	Neurology

A. Personal Statement

I am an associate professor of neurology at the University of Washington and a staff neurologist at the VA Puget Sound in Seattle. I have served as PI on 11 funded studies on the genetics of Parkinson's disease (PD) and have authored/co-authored nearly 100 papers on the topic of genetics and biomarkers in PD and related disorders. I also direct the Parkinson's Genetic Research Study (PaGeR) in Seattle, which over the past decade has enrolled ~1,300 PD patients from the Pacific Northwest. We have also recently enrolled a cohort of over 200 multiplex PD families from across North America and screened these families for mutations in known PD genes in anticipation of future gene discovery projects. I am currently Leader of the Analytical Core of the Pacific Northwest Udall Center (PANUC), and in the inaugural PANUC award, I led a project that successfully identified multiple genetic risk factors for cognitive impairment in PD. To support this endeavor, I spearheaded the formation of the PD Cognitive Genetics Consortium, which is composed of most of the existing Udall Centers and several non-Udall affiliated sites. This work required assembling and genotyping over 1,200 DNA samples for ~300,000 markers and merging and analyzing complex datasets across multiple sites. My laboratory maintains a bank of DNA and linked clinical data on over 10,000 subjects with neurodegenerative diseases, as well as controls, and we have participated in several large-scale international genetic studies. Finally, I have extensive experience in performing detailed clinical assessments and biospecimen collection of patients with PD. These qualifications make me well-suited to serve as a co-investigator on this application.

B. Positions and Honors

Positions and Employment

1994-1995	Intern, Department of Medicine, University of Washington, Seattle, WA
1995-1998	Resident, Department of Neurology, University of Washington, Seattle, WA
1998-1999	Postdoctoral Fellow, NIDA Clinical Research Program, Department of Psychiatry, Yale University and VA Connecticut Healthcare System, West Haven, CT
1999-2002	Postdoctoral Fellow, VA Neurosciences Program, Department of Psychiatry, Yale University and VA Connecticut Healthcare System, West Haven, CT
2002-2004	Staff Neurologist, Neurology Section, VA Puget Sound Health Care System, Seattle, WA
2002-2005	Acting Assistant Professor, Division of Neurogenetics, Department of Neurology, University of Washington School of Medicine, Seattle, WA
2004-present	Staff Neurologist, Geriatric Research, Education, and Clinical Center, VA Puget Sound Health Care System, Seattle, WA
2005-2010	Assistant Professor, Division of Neurogenetics, Department of Neurology, University of Washington School of Medicine, Seattle, WA
2010-present	Associate Professor, Division of Neurogenetics, Department of Neurology, University of Washington School of Medicine, Seattle, WA

Honors and Awards

1993	Alpha Omega Alpha Honor Society, School of Medicine, University of Miami
1994	Research Distinction in Neurology, University of Miami School of Medicine
2004	Fellowship Award, Winter Conference on Brain Research
2008	Resident Teacher of the Year Award, Department of Neurology, University of Washington

Professional Societies and Memberships

1996-present	American Academy of Neurology
1999-2011	Society for Neuroscience
2000-present	American Society of Human Genetics
2004-present	Seattle Institute for Biomedical and Clinical Research
2011-present	Movement Disorder Society
2012-present	American Neurological Association

C. Contribution to Science

1. Cognitive impairment is a common and debilitating problem in PD and approximately 80% of patients develop dementia during the course of the disease. The rate of cognitive decline and pattern of early cognitive deficits in PD are highly variable for reasons that are not well understood. I have led two large multicenter projects to determine whether genetic factors influence the risk for dementia and the specific pattern of cognitive deficits observed in PD. In our first project, which I co-led with Dr. Tsuang, the subcontract PI of the current proposal, we compared variation in selected genes in autopsied cohorts of patients with PD with dementia (PDD), dementia with Lewy bodies (DLB), and cognitively intact controls. We found that both *APOE* ε4 and *GBA* mutations substantially increase the risk for both DLB and PDD. Furthermore, *APOE* ε4 was associated with PDD and DLB even if the sample was restricted to cases with no or low levels of Alzheimer's disease (AD) pathology (neuritic plaques and neurofibrillary tangles), indicating that apoE might contribute to neurodegeneration through mechanisms unrelated to amyloid processing. In our second project, we examined the association between genetic variants and subject performance on specific psychometric tests in a large, longitudinally assessed PD cohort. We found that both *APOE* ε4 and *GBA* mutations predicted lower cognitive performance in PD but that the pattern of deficits differed. In non-demented patients, the effects of *APOE* ε4 were restricted to word list learning and semantic verbal fluency, a pattern that is consistent with the deficits seen in early AD. In contrast, mutations in *GBA* were primarily associated with lower performance in tests of working memory/executive and visuospatial function. These results represent an important first step in understanding the mechanisms underlying the heterogeneity of PD-related cognitive impairment.
    a. Tsuang D, Leverenz JB, Lopez OL, Hamilton RL, Bennett DA, Schneider JA, Buchman AS, Larson EB, Crane PK, Kaye JA, Kramer P, Woltjer R, Kukull W, Nelson PT, Jicha GA, Neltner JH, Galasko D, Masliah E, Trojanowski JQ, Schellenberg GD, Yearout D, Huston H, Fritts-Penniman A, Mata IF, Wan JY, Edwards KL, Montine TJ, **Zabetian CP** (2012). *GBA* mutations increase risk for Lewy body disease with and without Alzheimer's disease pathology. *Neurology* 79:1944-1950 (PMC3484986)
    b. Tsuang D, Leverenz JB, Lopez OL, Hamilton RL, Bennett DA, Schneider JA, Buchman AS, Larson EB, Crane PK, Kaye JA, Kramer P, Woltjer R, Trojanowski JQ, Weintraub D, Chen-Plotkin AS, Rick J, Irwin D, Schellenberg GD, Watson GS, Kukull W, Nelson PT, Jicha GA, Neltner JH, Galasko D, Masliah E, Quinn JF, Chung KA, Yearout D, Mata IF, Wan JY, Edwards KL, Montine TJ, **Zabetian CP** (2013). *APOE* ε4 increases risk for dementia in pure synucleinopathies. *JAMA Neurol* 70:223-228 (PMC3580799)
    c. Mata IF, Leverenz JB, Weintraub D, Trojanowski JQ, Hurtig H, Van Deerlin VM, Ritz B, Rausch R, Rhodes SL, Factor SA, Wood-Siverio C, Quinn JF, Chung KA, Peterson AL, Espay AJ, Revilla FJ, Devoto J, Hu SC, Cholerton BA, Wan JY, Montine TJ, Edwards KL, **Zabetian CP** (2014). *APOE, MAPT, SNCA*, and cognitive performance in Parkinson disease. *JAMA Neurol* 71:1405-1412 (PMC4227942)
    d. Mata IF, Leverenz JB, Weintraub D, Trojanowski JQ, Chen-Plotkin A,Van Deerlin VM, Ritz B, Rausch R, Factor SA, Wood-Siverio C, Quinn JF, Chung KA, Peterson-Hiller AL, Goldman JG, Stebbins GT, Bernard B, Espay AJ, Revilla FJ, Devoto J, Rosenthal LS, Dawson TM, Albert MS, Tsuang D, Huston H, Yearout D, Hu SC, Cholerton BA, Montine TJ, Edwards KL, **Zabetian CP** (2015). *GBA* variants are associated with a distinct pattern of cognitive deficits in Parkinson

disease. *Mov Disord* published online (doi: 10.1002/mds.26359) (NIHMSID 708985 / PMID 26296077)

2. In most instances Parkinson's disease (PD) is thought to arise from a complex interaction between genetic and environmental factors, each with relatively modest effects. Over the past decade my laboratory and our collaborators have elucidated several important genetic risk factors for PD using both candidate gene studies and genome-wide association studies (GWAS). These discoveries include common variants within the *MAPT, SNCA*, and *HLA* loci, and loss-of-function mutations in the *GBA* gene. These findings have subsequently been confirmed in GWAS meta-analyses and have provided important insights into the molecular pathophysiology underlying PD.
    a. **Zabetian CP**, Hutter CM, Factor SA, Nutt JG, Higgins DS, Griffith A, Roberts JW, Leis BC, Kay DM, Yearout D, Montimurro JS, Edwards KL, Samii A, Payami H (2007). Association analysis of *MAPT* H1 haplotype and subhaplotypes in Parkinson's disease. *Ann Neurol* 62:137-144 (PMC2836920)
    b. Mata IF, Samii A, Schneer SH, Roberts JW, Griffith A, Leis BC, Schellenberg GD, Sidransky E, Bird TD, Leverenz JB, Tsuang D, **Zabetian CP** (2008). Glucocerebrosidase gene mutations: a risk factor for Lewy body disorders. *Arch Neurol* 65:379-382 (PMC2826203)
    c. Hamza TH, **Zabetian CP**, Tenesa A, Laederach A, Montimurro J, Yearout D, Kay DM, Doheny KF, Paschall J, Pugh E, Kusel VI, Collura R, Roberts J, Griffith A, Samii A, Scott WK, Nutt J, Factor SA, Payami H (2010). Common genetic variation in the *HLA* region is associated with late-onset sporadic Parkinson's disease. *Nat Genet* 42:781-785 (PMC2930111)
    d. Mata IF, Shi M, Agarwal P, Chung KA, Edwards KL, Factor SA, Galasko DR, Ginghina C, Griffith A, Higgings DS, Kay DM, Kim H, Leverenz JB, Quinn JF, Roberts JW, Samii A, Snapinn KW, Tsuang DW, Yearout D, Zhang J, Payami H, **Zabetian CP** (2010). A *SNCA* variant associated with Parkinson's disease and plasma α-synuclein level. *Arch Neurol* 67:1350-1356 (PMC3010848)

3. To complement our discovery and validation of common genetic risk factors for PD, we recently initiated family-based studies. Using whole-exome sequencing, we identified a new mutation in the *RAB39B* gene that causes X-linked dominant PD. Subsequent *in vitro* experiments demonstrated that the mutation (p.G192R) results in mislocalization of the mutant protein, possibly by altering the structure of the hypervariable C-terminal domain that mediates intracellular targeting. Further characterization of normal and aberrant RAB39B function has the potential to elucidate important mechanisms underlying neurodegeneration in PD.
    a. Mata IF, Jang Y, Kim CH, Hanna DS, Dorschner MO, Witt J, Samii A, Chung KA, Shprecher DR, Espay AJ, Revilla FJ, Factor SA, Klepitskaya O, Higgings DS, Litvan I, Leverenz JB, Roberts JW, Agarwal P, Yearout D, Inca-Martinez M, Martinez E, Thompson TR, Cholerton BA, Hu SC, Edwards KL, Kim KS, **Zabetian CP** (2015). The *RAB39B* p.G192R mutation causes X-linked dominant Parkinson's disease. *Mol Neurodegener* 10:50 (PMC4581468)

4. Dopamine-β-hydroxylase (DBH) catalyzes the conversion of dopamine to norepinephrine, and circulating DBH protein levels vary widely among individuals. As a postdoctoral fellow, I discovered a functional polymorphism (rs1611115) in the promotor region of the *DBH* gene that accounts for approximately half of the total variation in plasma DBH levels. Many subsequent studies have examined the role of this common variant in psychiatric, neurological, and cardiovascular traits; it has been shown to associate with treatment response and specific symptoms (e.g., psychosis) in alcohol and cocaine abuse.
    a. **Zabetian CP**, Anderson GM, Buxbaum S, Elston RC, Ichinose H, Nagatsu T, Kim KS, Kim CH, Malison RT, Gelernter J, Cubells JF (2001). A quantitative trait analysis of human plasma dopamine β-hydroxylase activity: evidence for a major functional polymorphism at the DBH locus. *Am J Hum Genet* 68:515-522 (PMC1235285)
    b. **Zabetian CP**, Buxbaum S, Elston RC, Köhnke MD, Anderson GM, Gelernter J, Cubells JF (2003). The structure of linkage disequilibrium at the DBH locus strongly influences the magnitude of association between diallelic markers and plasma dopamine beta-hydroxylase activity. *Am J Hum Genet* 72:1389-1400 (PMC1180300)
    c. Kim CH, **Zabetian CP**, Cubells JF, Cho S, Biaggioni I, Cohen B, Robertson D, Kim KS (2002).

Mutations in the dopamine beta-hydroxylase gene are associated with human norepinephrine deficiency. *Am J Med Genet* 108:140-147

d. Chun LS, Samii A, Hutter CM, Griffith A, Roberts JW, Leis BC, Mosley AD, Wander PL, Edwards KL, Payami H, **Zabetian CP** (2007). DBH -1021C→T does not modify risk or age at onset in Parkinson's disease. *Ann Neurol* 62:99-101 (PMC2823266)

D. Research Support

Ongoing Research Support

2 P50 NS062684-07 Montine (PI) 08/01/2009 - 07/31/2020
NIH/NINDS
Pacific Northwest Udall Center, Analytical Core, Zabetian (PI)
The major goals of this core are to manage biospecimens (DNA, CSF, brain tissue) and linked clinical data, generate and analyze genetic and biomarker data, and provide statistical support for Udall Center research projects.
Role: Leader of Analytical Core

Research Grant Zabetian (PI) 05/01/2007 - 08/31/2016
American Parkinson Disease Association
Washington State Parkinson Disease Registry
This project will initiate and maintain a registry of PD patients who are willing to participate in research.
Role: PI

1 U01 NS082137-03 Zhang (PI) 09/30/2012 - 08/31/2017
NIH/NINDS
Large Scale Biomarker Discovery and Validation for Parkinson’s Disease
This project represents a cross-sectional, multi-cohort study to develop biomarkers for Parkinson’s disease that will help to identify and replicate diagnostic and progression biomarkers in CSF and plasma.
Role: Co-Investigator

Completed Research Support

5 R01 NS036960-13 Payami (PI) 03/01/1998-06/31/2015
NIH/NINDS
Genetic Analysis of Onset Age of Parkinson’s Disease
This project was a genome-wide association and gene-environment interaction study of Parkinson’s disease, that utilized study subjects from the NeuroGenetics Research Consortium.
Role: Co-Investigator

1 P50 NS062684-05 Montine (PI) 08/01/2009 - 09/30/2014
NIH/NINDS
Pacific Northwest Udall Center, Project 3, Zabetian (PI)
Genetic Risk Factors for Cognitive Impairment in PD
The major goals of this project were to determine whether common variation within the *APOE*, *MAPT*, and *SNCA* genes predicts risk of cognitive impairment or rate of cognitive decline in patients with PD.
Role: PI of Project 3

1 R01 NS065070 Zabetian (PI) 09/30/2009 - 06/30/2013
NIH/NINDS
Using Multiplex Families to Map Genes that Modify Susceptibility and Age at Onset in Parkinson's Disease
The major goal of this project was to collect a cohort of well-characterized multiplex PD families and to fine-map a previously reported linkage region for PD on chromosome 1.
Role: PI

1I01BX000531-04 Zabetian (PI) 10/01/2009 - 09/30/2013
Department of Veterans Affairs
Genetic Risk Factors for Parkinson's Disease
The major goal of this project was to validate findings from an ongoing genomewide association study on PD using next-generation sequencing and brain/CSF proteomic analyses.
Role: PI

1 R01 NS057567 Zhang (PI) 05/01/2008-04/01/2013
Biomarkers for Preclinical Parkinson's Disease

NIH/NINDS
This project sought to identify candidate CSF biomarkers in asymptomatic *LRRK*2 mutation carriers.
Role: Co-Investigator

International Research Program Grant Zabetian (PI) 03/11/2010 - 01/15/2013
Parkinson's Disease Foundation
Creating a South American Genetics Consortium on Parkinson's Disease
This project created a South American Genetics Consortium on PD which included six institutions in five countries (Argentina, Brazil, Colombia, Peru, and Uruguay).
Role: PI

5 K08 NS044138-05 Zabetian (PI) 08/19/2002 - 07/31/2008
NIH/NINDS
DBH as a Modifying Gene in Neurodegenerative Diseases
This project sought to determine whether a functional polymorphism in the dopamine beta-hydroxylase (*DBH*) gene was associated with DBH protein and mRNA levels in postmortem tissues, influenced transcriptional activation of the *DBH* gene, and was a risk factor for sympathetic nervous system dysfunction in PD.
Role: PI

Merit Review Award Zabetian (PI) 10/01/2005 - 9/30/2009
Department of Veterans Affairs
Analysis of *Nurr1* Variants in Familial and Sporadic Parkinson's Disease
The major goal of this project was to determine if variation within the *Nurr1* gene, which encodes a transcription factor critical to the survival of dopaminergic neurons, influenced susceptibility or age of onset in PD.
Role: PI

RESOURCES

LABORATORY:
Biospecimen preparation and storage: In approximately 100 sq. ft. of fully equipped laboratory space in both the VA Puget Sound and the 9th and Jefferson Building at UW Medicine adjacent to the UW Alzheimer's Disease Research Center (ADRC) evaluation and examination rooms for immediate processing and storage of plasma and CSF samples until they are shipped to the coordinating site.

Although UW is not directly conducting genetic analysis for the current proposal, we have the capacity to do so: Dr. Zabetian has 1,175 square feet of laboratory space. His laboratory routinely performs rapid processing of blood and CSF samples, DNA extraction from blood or tissue, high throughput genotyping of single nucleotide polymorphisms (SNPs) and microsatellites, and DNA sequencing. Facilities for RNA processing and quantification of gene expression using real-time RT- PCR are also present. Six -80° C freezers are available for long-term storage of CSF, DNA, RNA, and tissue samples.

CLINICAL:
Research participants are evaluated in clinic space at the University of Washington (UW) Medical Center and VA Puget Sound in Seattle.

In Seattle, UW Medicine has dedicated a newly renovated clinic in the recently completed Ninth and Jefferson Building (NJB). This clinic space includes five 150–sq. ft. examination rooms, four 200–sq. ft. interview rooms, a 300–sq. ft. waiting/administrative area, and two 200–sq. ft. rooms that have been newly remodeled into state-of-the-art cerebrospinal fluid (CSF) collection rooms w/ private bathrooms. We also have access to three 150–sq. ft. interview rooms and examination rooms and a 450– sq. ft. waiting/administrative area at this location.

At VA Puget Sound participants are evaluated in four 150–sq. ft. examination rooms, three 150–sq. ft. interview rooms, a 300–sq. ft. waiting/administrative area, and a 1,000–sq. ft. outpatient clinical research unit with three 2-bed rooms, which can be used for lumbar punctures.

The appropriate IRB approvals for the UW ADRC and PANUC are in place for recruitment of subjects at each of these sites. We will obtain additional approval for the proposed studies once funded.

COMPUTER:
All key personnel and staff members have networked desktop computers for data management, data analysis, manuscript preparation, and office-related uses and the use of laser printers, scanners, and fax machines. All computers have access to e-mail and the Internet, which allows personnel to use the computers from remote locations without requiring all staff members to be physically in one location in order to make use of computing resources. All faculty, staff, and students at the UW also have access to some disk space and daily computer time without charge on the central campus computers. These facilities are used primarily for electronic mail, transferring files, and using one of the many computer packages that are available but that are not used by a particular research group often enough to warrant paying for an annual license. Computer support staff is available at both UW and VA Puget Sound.

Genetic Analysis: Ten Dell desktop computers and a 4TB ATCS server. Software in rout ne use includes GeneMapper 4.0 (Applied Biosystems) for analyzing microsatellite data, SDS 2.4 (Applied Biosystems) and SNP Genotyping Analysis (Fluidigm) for SNP Genotyping Analysis, CopyCaller 2.0 (Applied Biosystems) for Copy Number Variation Analysis, Coffalyser.net (MRC Holland) for MLPA analysis and Mutation Surveyor (SoftGenetics) for sequence alignment and variant detection.

OFFICE:
All key personnel have offices at the UW Harborview Medical Center NJB or VA Puget Sound of approximately 150 sq. ft. each. Other staff members have adjacent cubicles in these two locations, including an additional 600 sq. ft. of shared office space at UW. All core personnel have access to file storage facilities.

Dr. Tsuang has offices at the Seattle division of the VA Puget Sound. Dr. Tsuang's office is located on the 8th floor of the VISN-20, Geriatric Research, Education, and Clinical Center **(GRECC)**, where she serves as Director. Her office is located approximately 7 miles away from the UW Medical Center, where she serves as Professor of Psychiatry & Behavioral Sciences in the School of Medicine. The study coordinator will have a cubicle at VA Puget Sound close to both Drs. Tsuang and Zabetian.

Dr. Zabetian has three offices at the VA Puget Sound and UW NJB for his use and that of his clinical research staff.

OTHER:
Secretarial services, equipment repair shop, computer support services, and medical media services are available at the VA Puget Sound and UW Harborview Medical Center. There are shared copy machines, fax machines, and laser printers available to all staff in proximity to their office space.

Administrative support for grant and budget management, purchasing, accounting, and human resources is provided by the Medicine Department of Psychiatry, in collaboration with all other participating UW Medicine Departments, and the Seattle Institute for Biomedical and Clinical Research (SIBCR), a nonprofit research and education organization at the VA Puget Sound Health Care System.

Research scientists have access to the UW library. They also have access to downloads of papers through SCOPUS, PubMed, Science Direct, IEEE, and other sources.

UW Medicine Institute for Translational Health Science, UW Medicine's NIH-funded CTSA, has exam rooms for both neurologic and cognitive testing. This resource is available for studies that are beyond the scope of routine subject visits.

UW Schools of Medicine and Public Health & Community Medicine: The UW is a hub of innovation and thought in a region that boasts one of the nation's top five states for business (Forbes.com) and knowledge-based economies (Information Technology and Innovation Foundation). With a diverse student body of over 47,000 full-time undergraduate and graduate students, including more than 2,600 international students from over 100 different countries; a workforce of over 40,000 faculty and staff members, including 6 Nobel Prize winners, 10 MacArthur grant fellows, and the 12th highest total of Academy members in the country; an annual operating budget in excess of $3 billion, and a thriving health system, the UW is easily one of the largest and most productive employers in the state.

Moreover, the university's commitment to research makes it an important force both in the Pacific Northwest and throughout the world. For example, in consecutive years, the UW has received over $1 billion in research funds, even during the recession, and the National Science Foundation has ranked the UW as the number one public institution in terms of receiving federal grants. The UW has also been an important destination for grant money from the American Recovery and Reinvestment Act (ARRA); since ARRA awards were first conferred in February 2009, the UW has received 406 awards totaling over $190 million, including 14 NIH GO Grant Awards ($30 million) and 23 NIH Challenge Grant Awards ($8.4 million). This productivity is a boon to the local economy, generating over $2 billion in business activity, supporting over 42,000 jobs statewide, and creating biological, medical, and software research advances that have led to the establishment of over 200 new technology companies, including Zymogenetics and ICOS.
Considering these achievements, it is no surprise that the UW is an internationally recognized leader in research in the genome sciences. For example, when the NIH created the first three National Centers of Excellence in Genomic Sciences, the UW received two of the three awards; three UW Medicine faculty were among the eight scientists worldwide recognized by the Gairdner Foundation for their seminal contributions to the Human Genome Project, and UW biomedical research programs have consistently ranked in the top three schools for receipt of NIH grant funding according to U.S. News & World Report. The UW continues to push the boundaries of science to advance findings in genomic science and is home to such cutting-edge facilities as outlined above. These facilities will support the proposed projects and advance the field forward ultimately toward improving clinical diagnosis and treatment of many debilitating diseases.

UW School of Medicine. The School of Medicine is renowned as one of the most outstanding biomedical research centers in the country, and is ranked second in the country in primary care medicine. Within the School of Medicine a number of different departments and programs have had interests in various aspects of the biology of aging, particularly the Department of Genome Sciences.
The Department of Psychiatry and Behavioral Sciences includes 250 faculty members, conducting research and providing clinical care at four locations: VA Puget Sound Health Care, UWMC, Children's Hospital and Harborview Medical Center. The department generates more than 36 million dollars in research grants and contracts per year and currently occupies over 10,000 square feet of bench laboratory space. The department includes seven main research divisions including addictions, child and adolescent psychiatry, geriatric, health services and psychiatric epidemiology, integrated care and public health, neurosciences, public health and justice policy.

VA Puget Sound, VISN-20 Geriatric Research Education Clinical Center: The VA Puget Sound is part of VISN-20, which includes facilities in Washington, Idaho, Oregon, and Alaska. The VA Puget Sound, a large-size affiliated tertiary care facility with over 400 authorized active beds, is the major referral center for the northwest Veteran population. It also serves as a teaching affiliate for the UW, uses state-of-the-art technology to provide health care that ranges from basic primary care to complex surgical procedures and to pursue important research questions among Veterans. Another key strength of the VA Puget Sound, particularly in relation to this project, is that investigators at this facility provide expert consultation in geriatrics and neurodegenerative disorders.

The GRECC provides infrastructures for the advancement and integration of research, education, and clinical achievements in geriatrics and gerontology into the VA health care system. At the VA Puget Sound GRECC, a world-class, interdisciplinary network of collaborators specialize in the identification of genes and pathways that cause AD and other forms of dementia as well as in the development and evaluation of therapeutic strategies to treat such neurodegenerative diseases. Dr. Tsuang was recruited to become the 4th Director of the GRECC in September 2012. One of her long-term goals for the GRECC is to establish a research focus on the genetics of neuropsychiatric and neurodegenerative disorders. The GRECC has over $7 million in research expenditures in FY13. Relevant to this proposal, the GRECC provides salary support for Dr. Tsuang and has assisted her to develop a mature research program in the genetics and intermediate phenotypes of schizophrenia.

Seattle Institute for Biomedical and Clinical Research (SIBCR): Drs. Tsuang and Zabetian are members of SIBCR, a nonprofit membership organization whose mission is to improve the health and well-being of Veterans through research and education conducted at the VA Puget Sound. SIBCR will provide resources such as grant and budget management, accounting, and HR support for SIBCR employees for this project through an established, proven administrative infrastructure.

EQUIPMENT:
The new clinical laboratory, examination, and evaluation space at UW Medicine is outfitted with new computer/printer system, refrigerator, -80 freezer, and a refrigerated centrifuge.

Genetic Analysis: The following major equipment is housed in Dr. Zabetian's Laboratory:

1) ABI PRISM 7900HT Sequence Detection System (TaqMan genotyping in 384-well format, real-time PCR)
2) ABI PRISM 3130 Genetic Analyzer (sequencing, microsatellite genotyping)
3) Fluidigm BioMark Nanofluidic real-time PCR instrument and loader (shared)
4) Four ABI 9700 GeneAmp PCR Systems (thermal cycler for PCR and sequencing reactions)
5) Two Revco, two Thermo, and two Dometic large capacity -80° C freezers for storage of DNA, RNA, CSF, plasma, serum, whole blood, and tissue.
6) NanoDrop ND-1000 Spectrophotometer (quantification of DNA and RNA)
7) Gel Logic 112 Electrophoresis Documentation and Analysis System (Carestream) (agarose gel imaging)
8) Two Sorvall Legend RT and one Jouan CR412 swinging-bucket centrifuges (processing of blood specimens and sample preparation).

Additionally, the UW ADRC has over two hundred x86 CPU cores dedicated for computation, primarily MS/MS sequence database searching (currently the SEQUEST, OMSSA, Mascot and X! Tandem algorithms available). An Nvidia workstation with two Tesla C1060 Computing Processors is also available in the Resource. Each of the two Tesla GPUs contains 240 processor cores and 4GB dedicated memory.

Data Management: Equipment available for data management as part the UW ADRC Biostatistics and Data Core includes:

Database Servers: The database servers include one 16-core Xeon analysis server, one16-core Opteron analysis & storage server, one quad-core Xeon storage server/NAS with 28 TB of RAID 5-equivalent storage, and one multi-purpose quad-core server. Workgroup SAS services for the EpiStats group will be provided via HP blade servers that store all non-OS data on an HP EVA enterprise SAN. These systems are hosted in a large data center located at the University. If a file server fails, another will be put in its place and the data will be re-presented to it. Two secondary/backup servers are located in the PANUC Data Core offices in the NJB Building. Each of these servers has the capability of handling multiple project functions (data entry, data storage, and/or data analysis [both Linux and Windows environments]) in order to efficiently handle project workloads and allow for project continuity if one or two servers fail.

Clinical data is entered into the database by site staff directly into site-specific databases on the storage server, via Remote Desktop Connection sessions over an SSH-encrypted network tunnel that uses keyed logins. The system can handle 30+ simultaneous users.

The UW controlled-access enterprise-level data center's network, power and environmental systems are monitored 24 hours a day, 7 days a week for disruptions. On-call staff are available for data center issue resolution. It is served by highly available city utility power, backup generators, and UPS service. Servers are protected by firewalls and not directly visible or accessible from outside the UW network.

Analytical Servers: Available analytical capability: 40+ CPU cores, as much as 228 GB RAM in one analysis server, and 30+ TB data storage space; a shared high performance computing cluster; Stata, R, PBAT, Eigenstrat, Merlin, Solar, Pedcheck, Plink and other software packages that are run in a mixed Windows and Linux environment.

Program Director/Principal Investigator (Last, First, Middle): Montine, Thomas J

CHECKLIST

TYPE OF APPLICATION *(Check all that apply.)*

☒ NEW application. *(This application is being submitted to the PHS for the first time.)*

☐ RESUBMISSION of application number: _____
(This application replaces a prior unfunded version of a new, renewal, or revision application.)

☐ RENEWAL of grant number: _____
(This application is to extend a funded grant beyond its current project period.)

☐ REVISION to grant number: _____
(This application is for additional funds to supplement a currently funded grant.)

☐ CHANGE of program director/principal investigator.

Name of former program director/principal investigator: _____

☐ CHANGE of Grantee Institution. Name of former institution: _____

☐ FOREIGN application ☐ Domestic Grant with foreign involvement List Country(ies) Involved:

INVENTIONS AND PATENTS *(Renewal appl. only)* ☐ No ☐ Yes

If "Yes," ☐ Previously reported ☐ Not previously reported

1. PROGRAM INCOME ***(See instructions.)***
All applications must indicate whether program income is anticipated during the period(s) for which grant support is request. If program income is anticipated, use the format below to reflect the amount and source(s).

Budget Period	Anticipated Amount	Source(s)

2. ASSURANCES/CERTIFICATIONS ***(See instructions.)***
In signing the application Face Page, the authorized organizational representative agrees to comply with the policies, assurances and/or certifications listed in the application instructions when applicable. Descriptions of individual assurances/certifications are provided in Part III and listed in Part I, 4.1 under Item 14. If unable to certify compliance, where applicable, provide an explanation and place it after this page.

3. FACILITIES AND ADMINSTRATIVE COSTS (F&A)/ INDIRECT COSTS. See specific instructions.

☒ DHHS Agreement dated: 4/23/15 ☐ No Facilities And Administrative Costs Requested.

☐ DHHS Agreement being negotiated with _____ Regional Office.

☐ No DHHS Agreement, but rate established with _____ Date _____

CALCULATION* *(The entire grant application, including the Checklist, will be reproduced and provided to peer reviewers as confidential information.)*

a. Initial budget period:	Amount of base $	18,651	x Rate applied	26.00%	% = F&A costs	$	4,848
b. 02 year	Amount of base $	18,651	x Rate applied	26.00%	% = F&A costs	$	4,848
c. 03 year	Amount of base $		x Rate applied	0.00%	% = F&A costs	$	
d. 04 year	Amount of base $		x Rate applied	0.00%	% = F&A costs	$	
e. 05 year	Amount of base $		x Rate applied	0.00%	% = F&A costs	$	
					TOTAL F&A Costs	$	9,698

*Check appropriate box(es):

☐ Salary and wages base ☒ Modified total direct cost base ☐ Other base *(Explain)*

☐ Off-site, other special rate, or more than one rate involved *(Explain)*

Explanation *(Attach separate sheet, if necessary.):*

4. DISCLOSURE PERMISSION STATEMENT: If this application does not result in an award, is the Government permitted to disclose the title of your proposed project, and the name, address, telephone number and e-mail address of the official signing for the applicant organization, to organizations that may be interested in contacting you for further information (e.g., possible collaborations, investment)? ☒ Yes ☐ No

UW Medicine
DEPARTMENT OF PATHOLOGY

5 January 2016

Walter A. Kukull, PhD
National Alzheimer's Coordinating Center
University of Washington
4311 11th Avenue NE #300
Seattle, WA 98105

Dear Dr. Kukull,

I am writing to express my support for the collaborative grant application entitled "Plasma biomarkers in Lewy Body Disease," which is being submitted for funding by the National Alzheimer's Coordinating Center.

As Director of the University of Washington ADRC, I am endorsing the participation of our Center in this project, and Dr. Tsuang as the Site Investigator.

We confirm that all Key Personnel listed in this application have received appropriate training in the responsible conduct of research, as mandated by DHHS.

We are pleased to contribute to an increased understanding of this important topic, and we look forward to participating in a scientifically productive project.

If you have questions regarding the enclosed information, please contact Molly Chinn at wamble@uw.edu or 206-277-3281.

Sincerely,

Thomas J. Montine, MD, PhD
Director, UW Alzheimer's Disease Research Center
Alvord Professor and Chair
Department of Pathology

Thomas J. Montine, MD, PhD
Alvord Professor and Chair
Department of Pathology
University of Washington
tmontine@uw.edu
http://sites.google.com/site/montinelab

SPECIFIC AIMS

The purpose of this project is to collect the requisite data and build the necessary collaborative relationships to submit a grant for a large-scale prospective study of the utility of blood-based biomarkers in Lewy Body disease (LBD). *The long-term goal of this line of research is the generation of blood-based profiles that have diagnostic, prognostic and theragnostic value in LBD.* Given the rapidly growing elderly population, neurodegenerative dementias are a major public health problem. LBD is the 2nd most prevalent neurodegenerative dementia accounting for 15-20% of cases and is often misdiagnosed as Alzheimer's disease (AD). LBD is an α-synuclein disorder that is characterized by Lewy Body and Lewy neurites in specific areas of the brain as well as acetylcholine neuronal degeneration. There is frequent AD and LBD overlap making the differential diagnosis between LBD and AD a significant problem in clinical practice. Additionally, there is an urgent need for methods to predict clinical course in LBD to design trials and monitor interventions. Based on preliminary findings it is our hypothesis that a blood-based biomarker profile can be accurate in detecting and distinguishing LBD from AD and controls.

Our team has previously developed a blood-based screening tool for AD that has been validated across cohorts, tissues, assay platforms, species and ethnicities. We also have demonstrated that our methods can detect Parkinson's disease (PD) and discriminate PD from AD. In beginning to test the current hypothesis, we conducted two pilot studies from two independent NIA-funded Alzheimer's disease centers (ADCs; UTSW and Mayo Clinic). In the first study (UTSW), proteomic analyses were conducted using stored blood samples from 189 patients (11 LBD, 18 fronto-temporal dementia (FTD), 50 AD, 49 PD and 11 Down syndrome (DS) and 50 controls). Using support vector machine analyses (SVM), our algorithmic approach was >98% accurate in distinguishing LBD from other neurodegenerative diseases. Next blood samples from 122 patients (LBD n=35, AD n=38, control n=48) was analyzed from Mayo Clinic Jacksonville. Again, our proteomic profile was highly accurate in detecting and discriminating LBD from AD and controls (100%). Additionally, our team has shown that plasma ceramides (C16:0; C18:1; C20:0 and C24:1) and monohexylceramides (C18:1, C24:1) are significantly altered in LBD and AD as compared to controls. Therefore, we hypothesize that combining these blood based biomarkers will be accurate in detecting LBD and distinguishing LBD from other neurodegenerative diseases. More recently we have generated a proinflammatory endophenotype that is present among 30% of LBD and 15% of AD cases. Among AD cases, the proinflammatory endophentoype (1) predicts poorer cognition and (2) predicts treatment response within a previously conducted NSAID clinical trial. Among LBD cases, the proinflammatory endophenotype was associated with poorer memory and verbal fluency. Here we propose to identify biologically relevant subgroups of LBD cases and determine how these subgroups impact clinical course, which may have implications for precision-based therapeutics. This proposal leverages three currently-funded Alzheimer's disease centers (Mayo [Rochester and Jacksonville], UW and UTSW), cutting edge laboratories in blood-based biomarkers of neurodegenerative disease (UNTHSC; Mayo Rochester) and the NACC data center to address the following Specific Aims:

Specific Aim 1: Replicate our blood-based profile of LBD in a larger sample. Here we will collect plasma samples from n=100 LBD cases, n=50 AD cases, 50 PD cases, 50 RBD cases and n=50 controls from the ADC sites. First, we will compare levels of blood biomarkers (proteomics and ceremides/monohexylceramides) across diagnostic groups. Next we will utilize support vector machine (SVM) methods to replicate our blood-based profile for the detection of LBD and discrimination of LBD from other groups.

Specific Aim 2: To identify biologically-based subgroups in LBD. Here our blood-based biomarkers will be utilized to generate LBD subgroups based on sphingolipids, inflammation, vascular function and metabolic pathways based on our prior methods. We will compare the presence of these subgroups in LBD to other neurodegenerative diseases and determine if these subgroups are related to different clinical phenotypes For example, acetylcholinesterase inhibitor responders as in our pilot study.

Exploratory Aim 1. To examine the biological profile of RBD. Here we will compare blood based profiles of RBD to other diagnostic groups to determine if alterations occur early in the process prior to the onset of LBD.

A. SIGNIFICANCE

A.1 Detecting & Diagnosing Lewy Body Disease. Lewy Body disease (LBD) is the second most common degenerative disease causing dementia. The disease was first recognized by Kosaka[1] and brought to clinical attention by McKeith[2]. In a large all-cause dementia autopsy series[3], 25% have Lewy Body pathology. When patients are recognized as having the consensus criteria for LBD they commonly have Lewy Body pathology[4] and when there is probable Rapid Eye Movement Behavior Disorder (pRBD) then LB pathology is very likely[5]. However those with Lewy Body pathology are often not recognized clinically as having LBD[6]. One of the reasons for this is the overlapping Lewy Body and Alzheimer (AD) pathology and the more extensive the tau pathology, the harder it is to recognize the Lewy Body clinical component. Multimodality imaging is good at separating LBD from AD but is expensive[7]. A recent genetic study shows an equal overlap of LBD with PD and AD when excluding ApoE. [8] A blood-based biomarker would provide a cost- and time-effective means for detecting LBD and separating LBD from AD. These profiles could also be evaluated in patient with mild or pre-disease such as isolated RBD which may precede LBD by years[9]. Therefore, there remains a significant need to improve the accuracy of detecting LBD cases at the earliest possible time- point[10]. It is our hypothesis that blood-based biomarkers have diagnostic, prognostic and theragnostic promise in LBD.

A.2 Diagnostic Biomarkers of Neurodegenerative Disease. A major impediment to development of treatments and clinical trials for neurodegenerative diseases is the lack of sensitive, easily-obtained diagnostic biomarkers[11-15]. The diagnosis of these diseases remain based on clinical symptoms[16] with newer diagnostic criteria attempting to incorporate biomarkers[17]. The search for biomarkers that have diagnostic and prognostic utility in neurodegenerative diseases has grown exponentially[12,18,19] with the majority of work focusing on neuroimaging and cerebrospinal fluid (CSF) methodologies[10,12,18-21]. While advanced imaging and CSF methods have tremendous potential as diagnostic biomarkers of neurodegenerative diseases, accessibility and cost barriers preclude these from being utilized as the first step in this process[13,14,22].

A.3. Biomarkers of LBD. There is a great need for biomarkers of LBD[14,15,22] with no biomarkers currently validated[23]. Reliable biomarkers of LBD could have many uses, including early and pre-clinical diagnosis, tracking disease progression, identification and development of disease-modifying treatments, identifying surrogates for therapeutic outcome measures, and identifying disease endophenotypes[15,22]. To date, most of the research seeking to identify biomarkers of LBD, have focused on imaging[10,20,21,24] and CSF[14,22,25-27] approaches. However, these methods are not viable candidates for wide-spread use due to cost, invasiveness and limited availability[28,29]. In fact, it has been proposed that biological markers of LBD should be "cheap, reliable and reproducible, and make use of biological samples that are easy to obtain"(pg. 1)[14]; blood-based biomarkers would fulfill these proposed criteria. Additionally, it has been proposed that *proteomic biomarker profiling* is a promising method for discovering LBD biomarkers[22,23] as a battery of markers covering a range of biological processes may be required to address the needs of such complex disorders[30]. In fact, profiling analytes associated with multiple disease may highlight novel biological pathways for therapeutic interventions in the dementia syndromes[31]. Our work on blood-based biomarkers of AD has consistently shown that a multi-marker approach identifying biomarker profiles of disease presence can yield excellent results[28,29,32]. Here we propose that our blood-based biomarker profile can (1) detect LBD, (2) discriminate LBD from other neurodegenerative diseases and (3) identify biologically relevant subgroups of LBD cases.

A.4 Biological Subgroups in LBD. A large number of clinical, basic and epidemiological studies have linked inflammation to neurodegenerative diseases, including LBD. Additionally, it has been proposed that profiling inflammation may provide novel therapeutic interventions for neurodegeneration[33,34]. In our prior work, we have identified a subgroup of LBD cases where inflammatory pathways were significantly altered. This proinflammatory endophenotype was also related to poorer cognition. Here we propose to identify multiple biologically-based subgroups of LBD and determine how these subgroups may offer novel therapeutic entry points for precision-based medicine in LBD.

B. INNOVATION

This project is highly innovative for several reasons. ***[Blood Biomarker Profiles of LBD]*** There are no currently available validated biomarkers of LBD. Our multi-marker proteomic and lipid profile approach is highly innovative and has yielded excellent results in Alzheimer's disease. ***[Biologically-Based LBD Subgroups]*** The identification of specific subgroups of LBD cases that are likely to respond to particular therapy (i.e.

precision medicine) is highly innovative. In our prior work, we have shown that our proinflammatory endophenotype identifies a specific subset of AD patients where inflammation is of particular importance and are most likely to benefit from NSAID therapy. If validated, our approach to the identification of select subsets of LBD cases based on specific biological profiles would set the stage for a precision-based medicine approach to the development of novel therapeutics for this devastating disease. This is a significant departure from the 1-drug-1-disease approach currently in place for LBD; however, subgroup approach is what transformed the fields of cardiology and cancer and has led to significant cure rates for these diseases. **[Combining Proteomics and Sphingolipid Biomarkers Analyses]** The current will combine expertise in multiple lines of blood-based biomarker analyses to profile LBD in a manner that has not been accomplished to date. **[Leveraging the Power of Multiple ADCs]** The current project sets the stage for a large-scale collaboration across multiple ADCs to prospectively study novel biomarkers of LBD.

C. APPROACH

C.1. Introduction By leveraging multiple currently funded Alzheimer's disease centers (ADCs), the current project will cost-effectively (1) generate a blood-based method for detecting LBD and discriminating LBD from other neurodegenerative diseases, (2) identify biologically-based subgroups of LBD that have potential for novel precision-based medicine therapeutics, and (3) conduct preliminary analyses of the biological profiles of RBD, a pre-LBD state identified in many patients.

C.2 Preliminary Data.

A Blood-Based Proteomic Method for Detecting AD. The current team has extensive experience investigating biomarkers of neurodegenerative disease, beginning with AD[19,28,29,35,37-44]. To date, the current group is ***the only*** to have followed the "fit-for-purpose" biomarker validation methods[45,46] and done each of the following: (1) generated the algorithm of AD on a discovery-based assay platform[28,35], (2) validated the AD algorithm across multiple independent cohorts[29,47], (3) validated the AD algorithm on an independent assay platform[36,47], (4) validated the AD algorithm in human and animal models[36], and (5) validated the algorithm across ethnicities[47,48].

Table 1. Diagnostic Accuracy of Blood Markers of AD	AUC	Sensitivity	Specificity
108 protein algorithm[28]	0.95	0.94	0.84
30-protein algorithm[35]	0.94	0.89	0.85
ADNI validation[29]	0.89	0.75	0.91
CSF biomarker accuracy comparison [29]	0.92	0.84	1.00
21-protein algorithm[36]	0.98	0.95	0.90

Sphingolipids in AD. Our team also has extensive experience studying the link between sphingolipid alterations and AD[49-53]. In a longitudinal study of 120 AD patients, higher sphingomyelins (SM)/ceramide and dihydrosphingomyelin (DHSM)/dihydroceramides (DHCer) ratios dose-dependently predicted slower progression[52]. In independent studies, sphingolipid transport was altered in plasma and CSF of AD cases as compared to controls[50] and CSF levels of ceramide and SM correlated with CSF levels of amyloid and tau[49]. Based on this work, and that of others, Mielke et al have proposed that sphingolipid pathway may have diagnostic and therapeutic implications for AD[51,53,54].

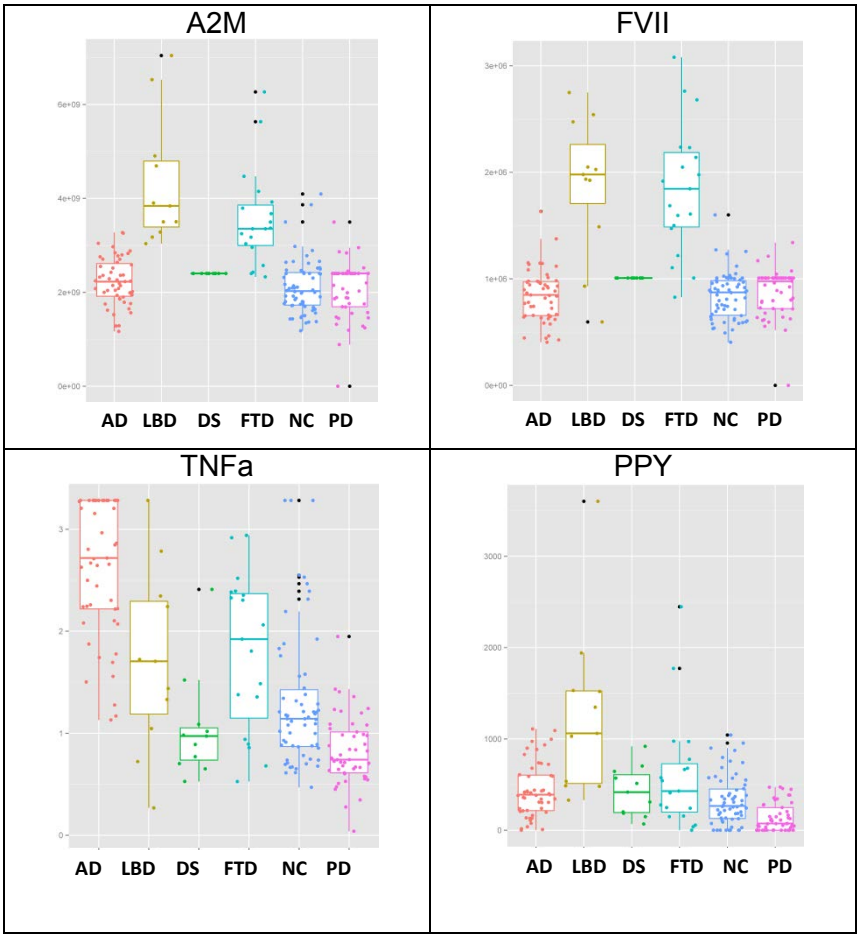
Blood-Based Biomarkers of LBD. Analyzing data to test our current hypothesis, we conducted two pilot studies utilizing previously plasma samples from two independent ADCs (UTSW, Mayo Jacksonville).

UTSW Proteomics Pilot Study. Proteomic markers from our AD algorithm were assayed for 203 patients: Down syndrome n=11, PD n=49, LBD n=11, FTD n=19, AD n=51 and normal controls n=62. When plotted against one another, the mean levels and relative profiles of specific proteomic markers were significantly different across groups (**Figure 1**). For example, pancreatic polypeptide and alpha-2-macroglobulin were significantly elevated in LBD as compared to all other groups. Further, TNFα was most elevated in AD and lowest in PD. Next, support-vector machine (SVM) models were generated that take into account the over and under expression profiles of each marker simultaneously across diagnostic groups. The SVM-based algorithm was >98% accurate in classifying all patients (O'Bryant et al manuscript under review).

Mayo Jacksonville Proteomics Pilot Study. Next, we conducted a second pilot study to replicate the findings in an independent cohort. Plasma samples from 122 patients (LBD n=35 all responsive to acetylcholinesterase inhibitors which indicates patients likely had less tau pathology[55], AD n=38, control n=48) were assayed from Mayo Clinic Jacksonville on the same proteomic markers. Using SVM analyzes, our proteomic profile was 100% accurate in discriminating LBD from AD and controls. Therefore, our preliminary analyses suggest the following: (1) a proteomic profile can be generated that detects LBD and (2) this multi-marker – multi-classification approach can discriminate LBD from other neurodegenerative diseases.

Mayo Rochester Sphingolipids Pilot Study. Sphingolipids were measured from age- and sex-matched groups of autopsy confirmed DLB (n=26), AD (n=18) and controls (n=21) using ESI/MS/MS. LBD and AD groups had higher plasma levels of ceramides C16:0 (p = 0.011), C18:1 (p = 0.006), C20:0 (p = 0.005) and C24:1 (p = 0.011) and of monohexosylceramides C18:1 (p = 0.003) and C24:1 (p = 0.004) when compared to controls (Mielke et al manuscript under review). These results support previous cellular research and suggest that plasma ceramides and monohexosylceramides are elevated in individuals with dementia and either LB or Alzheimer's pathology.

Figure 1 – Blood biomarker profiles for select proteins across neurodegenerative diseases. Note that overall profile varies across diseases. As an example, AD was statistically different than LBD in opposite direction across all 4 proteins. AD was similar to FTD in PPY levels, but significantly different on all other markers. AD and PD were significantly different on TNFa and PPY but similar on A2M and FVII. Using support vector machine (SVM) analyses, these differences in protein levels across diseases led to 100% accuracy in discrimination. Midpoint of box plots represents mean protein values.



Blood-Based Subgroups of AD. In our prior work, we have proposed the existence of proinflammatory and metabolic endophenotypes that can be identified via blood-based proteomics and represent subgroups of AD cases where inflammation and/or metabolic dysfunction is of key importance[37,48]. We have also identified a depressive endophenotype of AD[56,57]. In digging deeper at the proinflammatory endophenotype, we conducted a series of studies to characterize and understand the clinical impact of this subgroup of AD cases. The proinflammatory endophenotype has been generated using multiple methods, including random forest analyses, clustering analyses, and PCA using multiple markers (CRP, IL5, IL6, IL7, IL10, and TNFα) across multiple assay platforms (ELISA, ECL, Luminex). Analyzing data from 200 AD cases and 200 controls, the proinflammatory endophenotype was generated and split into 3 groups, with those having low inflammation being in the low group (15% of AD cases), those with broadly normal inflammation (middle group, 70% of AD cases) and those with consistently high levels of inflammation (15% of AD cases). Among AD cases, the high end of the proinflammatory endophenotype was associated with significantly poorer MMSE scores (p<0.001), higher CDR scores (p<0.001), poorer memory (p<0.001) and language abilities (p<0.005)(O'Bryant et al manuscript under review). We then identified the presence of the proinflammatory endophenotype in a 3XTg animal model of AD (60% of diseased animals). Next, we conducted proof-of-concept analyses of the ADCS AD anti-inflammatory trial[58] to test our hypothesis that the proinflammatory endophenotype would predict treatment response[59]. Of the 351 patients enrolled, a total of 156 had viable baseline plasma samples and all requisite clinical outcome data. Plasma inflammatory markers were assayed via ECL (CRP,TNFα, IL5, IL6, IL7, IL18 & IL10). The total sample was split into the following groups based on

response: (1) responder (i.e. MMSE improvement over 12mo), (2) stable (no change in MMSE over 12mo), (3) non-responder (MMSE decline of 1-2 points) or (4) adverse responder (MMSE decline ≤ 3 points). Using support vector machine (SVM) analysis, over 90% of the entire sample was correctly classified using the proinflammatory endophenotype. Next the analyses were re-run by arm, with > 98% correct classification per arm. When looking more closely at the naproxen arm, those with elevated scores on the proinflammatory endophenotype who were treated with naproxen demonstrated significantly *less cognitive decline* on MMSE scores over 12mo as compared to the placebo treated group ($F[1,6] = 8.2$, $p=0.02$). In fact, 63% of the patients in the naproxen treatment group improved or remained stable.

Characterizing the Proinflammatory Endophenotype in LDB. Next we examined the proinflammatory endophenotype in LBD as compared to AD. The prevalence of the high end of the proinflammatory endophenotype was 15% in AD = 15% and 30% of LBD cases. Across both AD and LBD, the high end of the proinflammatory endophenotype was associated with significantly increased medical comorbidities, poorer memory and verbal fluency (**Table 5).**

Table 2 – Characteristics of patients in the high end of the proinflammatory endophenotype

Diagnosis	Age	Education	CoMorbid	CERAD	Animals
AD Low (n=150)	75.5(7.4)	14.5(3.7)	1.0(0.8)	6.2(1.3)	10.5(2.3)
Middle	77.1(8.5)	13.5(4.2)	1.6(1.5)	4.0(3.4)	9.0(4.0)
High	80.1(7.9)	13.0(1.1)	2.2(2.4)	1.3(1.2)	7.5(2.1)
LBD Low (n=15)	69.4(1.0)	15.2(3.0)	1.4(0.3)	11.2(1.1)	15 (4.2)
Middle	75.5(4.4)	14.5(2.1)	1.8(0.7)	9.2(2.3)	16 (21)
High	78.9(2.0)	12.0(1.0)	2.5(1.2)	5.2(1.4)	7 (2.2)

NOTE: CERAD = memory measure, list learning total scale scores where the population mean = 10, sd=3; comorbidities = average number of comorbidities (diabetes, obesity, dyslipidemia, hypertension); Animals = verbal (semantic) fluency, total number of animals generated within 60s

Summary of Preliminary Data for Specific Aim 2. In our preliminary work, we (1) generated a proteomic profile that is highly accurate in detecting LBD and discriminating LBD from other neurodegenerative diseases, (2) demonstrated that sphingolipids are significantly altered in LBD as compared to controls, (3) identified a proinflammatory endophenotype that is present in LBD and (4) demonstrate that the proinflammatory endophenotype is associated with poorer cognition among LBD cases.

C.3 Participants. A total of 300 participants will be included that are already enrolled and actively followed by the 4 participating ADC sites (LBD n=100, pre-LBD n=50, AD n=50, PD n=50, control n=50). Each site will recruit 25% of patients over a two year period. All patients will have the National Alzheimer Coordinating Center (NACC) data collected as is in typical ADC patients. In addition they will have the data collected from the Lewy Body Battery that is under development (a prototype will be available from July 2016). All data will be entered into the NACC data base.

Exclusion Criteria – (1) presence of current cancer or current uncontrolled inflammatory condition (e.g. urinary tract infection) at the time of blood draw, (2) actively taking anti-inflammatory medications, (3) history of recent cancer, (4) recent traumatic brain injury with loss of consciousness, (5) current/recent alcohol/substance abuse, (6) active severe medical condition (e.g. CKD/ESRD, dialysis, CHF, COPD). **Inclusion definitions and criteria** – LBD cases will meet the McKeith criteria[60] for probable LBD. The pre LBD cases will have documented RBD by polysomnography or their caregiver will confirm that they act out their dreams at night. The AD patients will meet McKhann criteria[61]. Idiopathic PD diagnosis will be confirmed by a Moment Disorder specialist, which has a high correlation with pathological PD[62]. The controls will be cognitively normal and have no parkinsonism, RBD or hallucinations.

Blood Collection Procedures. PI O'Bryant is the lead of an international working group that generated guidelines for the standardization of pre-analytic processing of samples for studies examining blood-based biomarkers of AD[63], which will be followed. Briefly, blood will be collected as follows: (1) fasting blood collected using 21g needle, (2) sample tubes collected in the following order – blood culture tube, coagulation tube, serum, heparin, plasma EDTA tube, (3a) serum tube allowed to clot for 30 minutes at room temperature in a

vertical position, (3b) plasma tubes gently inverted 5-10 times, (4) centrifuged with horizontal rotor for 10 minutes at 2000 x g within one hour of collection, (5) 250 uL aliquots of serum will be transferred into polypropylene (cryovial) tubes, (6) sample ID (Freezerworks™ barcode labels) affixed to each aliquot, and (7) samples placed into -80º C freezer within 2 hours of collection.

Proteomic Assays. Serum samples will be assayed in duplicate via a multi-plex biomarker assay platform using electrochemiluminescence (ECL) on the QuickPlex SQ 120 imager from Meso Scale Discovery (MSD; http://www.mesoscale.com) per our previously published protocols[36,64]. ECL technology uses labels that emit light when electrochemically stimulated, which improves the sensitivity of detection of many analytes at very low concentrations. ECL measures have well-established properties of being more sensitive and requiring less volume than conventional ELISAs[65], the gold standard for most assays. The proteomic markers to be assayed include are from our previously validated AD profile[36], which also discriminated AD from PD as well as DLB from AD in our preliminary work: FABP, beta 2 microglobulin, PPY, CRP, PYY, GLP-1, VCAM1, thrombopoeitin, lipoprotein a, α2 macroglobulin, exotaxin 3, tumor necrosis factor α, monocyte chemotactic protein 1, tenascin C, angiopoietin, CA19.9, CA125, interleukin (IL)-5, IL6, IL7, IL10, IL18, adiponectin, I309, Factor VII, VCAM 1. We will also assay α-synuclein and DJ-1, which have been successfully assayed on the MSD platform. Internal QC protocols are implemented in addition to manufacturing protocols including assaying consistent controls across batches, analysis of impact of protocol variability, and assay of pooled standards across lots.

Sphingolipid Assays. The sphingolipid analyses will be conducted by the Mayo Clinic Metabolomics Core, one of six NIH Common Fund-supported metabolomics center in the United States.
Plasma ceramides, sphinganine, sphingosine, sphingosine-1-phosphate (S1P), will be measured by previously described technique[66]. Briefly a 25ul aliquot of plasma is spiked with internal standards mixture prior to undergoing extraction. Data acquisition is done using select ion monitor (SRM) after chromatographic separation and electron ionization on the Thermo TSQ Quantum Ultra mass spectrometer (West Palm Beach, FL) coupled with a Waters Acquity UPLC system (Milford, MA). Concentrations of each analyte are calculated against each perspective calibration curve. Glucosylceramides and galactosylceramides are quantified on a Sciex 6500 (Framingham, MA) equipped with a SelecION interface to further separate the two forms of hexosyl ceramides after the initial chromatographic separation on a TX2 Cohesive Liquid Chromatograph system (Thermo Fisher, Waltham, MA). Briefly 50ul aliquot of plasma is spiked with internal standards mixture prior to undergoing extraction. Data acquisition is done using select ion monitor (SRM) via electron ionization. Concentrations of each analyte are calculated against each perspective calibration curve.

C.4 Statistical Analyses. Analyses will be performed using R (V 2.10) statistical software[67] and SPSS 19 (IBM). **Biomarker data preprocessing -** Blood biomarker data will first be transformed using Box-Cox transformation. . **Batch effect detection and normalization and pre-analytic variables -** We have yet to identify any significant batch effects while using the MSD platform. We continue to minimize batch effects by (1) following well-defined protocols (2) utilizing quality control samples in each batch, which will allow detailed cross-batch normalization to reduce the batch effect. In addition, we will use clustering method to detect whether the batch effects (and processing variables) are still present and/or relevant. If present, we will use DWD (distance weighted discrimination)[68] and CAMBAT (Combining batches) methods to remove the effects[69]. For the sphingolipids, internal standards of all lipids are used.

Specific Aim 1: Validate our blood-based profile of LBD.
Hypothesis 1: Plasma proteomic and sphingolipid markers will be significantly altered in LBD as compared to AD, PD and controls.

- To test this hypothesis, ANCOVA will be utilized with diagnosis as the grouping variable and proteomics/sphingolipids as the predictor variables. Multivariate models will adjust for age, sex, education, medical comorbidities and APOE4 status.

Hypothesis 2: Our blood-based algorithm will be highly accurate in detecting LBD (AUC>0.80)

- To test this hypothesis, support vector machine (SVM) multi-classification analyses will be utilized. Our blood-based markers (proteomics and sphingolipids) will be included as the predictor variables in the classification with diagnostic group as the output in the classification (LBD, PD, RBD, AD, control).

Exploratory analyses: In additional analyses, we will utilize regression models to examine the associations between the protein and sphingolipid levels and clinical measures of LBD, AD, and PD including cognitive, functional, motor, and behavioral measures. This information will help to determine whether the markers of interest are associated with disease severity and specific clinical phenotypes of each disease.

Sample Size & Power. The proposed sample size will provide an observed power of 0.90 with alpha = 0.05 to detect a medium effect size (f=0.25) for detecting the hypothesized effect in Hypothesis 1. For Hypothesis 2, SVM will be utilized. SVM is ideal for multi-classification (superior to random forest [RF] analyses) of all diagnostic groups and is based on the concept of decision planes that define decision boundaries and is primarily a classifier method that performs classification tasks by constructing hyperplanes in a multidimensional space that separates cases of different class labels. Per Institute of Medicine (IOM) guidelines, the cohort will be randomly divided into Training and Test sets[70]. Using MedCalc, the proposed sample size will provide an observed power of 0.90 with alpha = 0.05 to detect our proposed effect size (AUC>0.80).

Specific Aim 2: To identify biologically-based subgroups in LBD.
Hypothesis 3: We hypothesize that our proinflammatory endophenotype will be associated with worse cognition and more rapid disease progression in LBD.

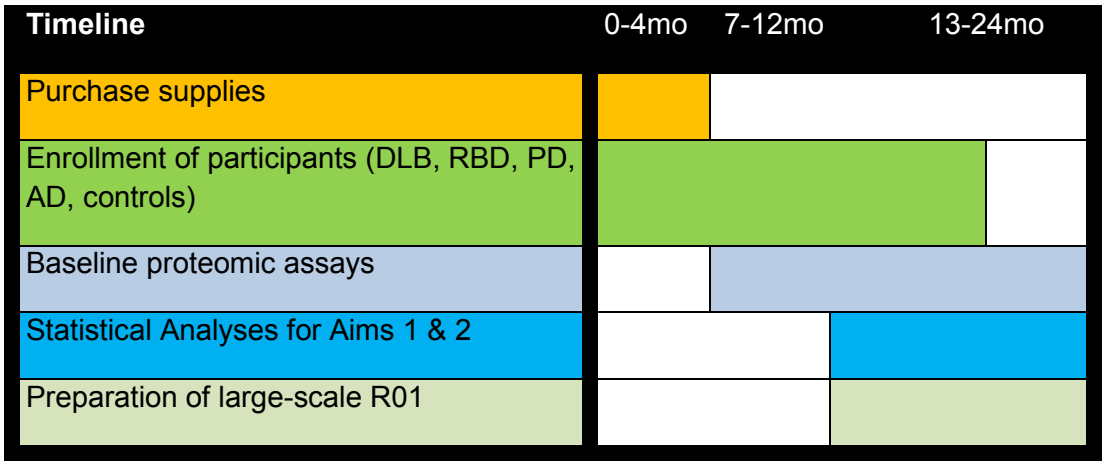
- First, our proinflammatory endophenotype will be generated using SVM-based methods with cut-scores from our previously conducted work. Next, the endophenotype groupings (high, normal, low) will be entered into an ANCOVA as the grouping variable with neuropsychological test scores as the outcome variable; age, gender and education will be entered as covariates.
- Exploratory analyses will be conducted to identify additional endophenotypes based on metabolic profiles and sphingolipid levels. In our prior work, we have identified multiple endophenotypes within AD cases including a proinflammatory endophenotype, metabolic endophenotype, neurotrophic endophenotype, oxidative stress endophenotype and a depressive endophenotype.

Sample Size & Power. In all of our prior work, the proinflammatory endophenotype has been associated with a medium-to-large effect size. Assuming a medium effect size, the proposed sample will provide an observed power of 0.80 with alpha = 0.05 to detect the proposed effect.

Exploratory Aim 1. To examine the biological profile of RBD. Here we will compare blood based profiles of RBD to other diagnostic groups to determine if alterations occur early in the process prior to the onset of LBD.

- Exploratory analyses will be conducted comparing proteomic and sphingolipid levels of RBD cases as compared to LBD, AD, PD and controls using ANCOVA.

The current project will provide very unique data regarding blood-based biomarkers in LBD. This information will be utilized, along with the collaborative infrastructure generated, to submit a larger R01 to further this line of research.


Timeline
0-4mo
7-12mo
13-24mo
Purchase supplies
Enrollment of participants (DLB, RBD, PD, AD, controls)
Baseline proteomic assays
Statistical Analyses for Aims 1 & 2
Preparation of large-scale R01

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